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Inhibition of PI3K/Akt/mTOR Signaling Pathway by Vitis Vinifera Phytocompounds: A Promising Strategy for Supressing Colorectal Cancer Growth and Metastasis

Alan S Mathew*

Abstract

Objectives: *Colorectal cancer was not typically identified a few decades ago. Today, with almost 900 000 fatalities each year, it is the fourth most dangerous cancer in the world. Colorectal cancer is responsible for about 10% of all cancer diagnoses annually and cancer-related deaths worldwide. It is the second most common type of cancer in women and the third most common type in men. Incidence and death are roughly 25% lower in women than in men. The PI3K/AKT/mTOR signaling system, which controls a wide range of cellular functions including survival, growth, angiogenesis metabolism, proliferation, and metastasis, is hyperactivated or changed in many cancer forms. Hence these proteins may be considered as therapeutic targets to supress colorectal cancer. In this study, the targeted proteins implicated in the etiology of various malignancies were examined for their pharmacological properties and therapeutic impact using the phytochemical components of Vitis vinifera.* ***Methods:*** *In this study, 203 phytochemicals from Vitis vinifera were selected to evaluate their compatibility with the PI3K, AKT, and mTOR target proteins. A virtual tool called PyRx was used to carry out the molecular docking. Data and molecular structures of the phytocompounds and proteins obtained from Indian medicinal plants, phytochemistry, and therapies, as well as PubChem, were used in the computer analysis. Several technologies, such as BIOVIA discovery studio software and PDBsum generator, were used to validate the protein structure. Using ADMET filters, the ligands' pharmacological evaluation was performed.* ***Result:*** *According to the results of molecular docking, the ligands Lupeol, 4-[(2R,3R)-3-(3,5-dihydroxyphenyl)-6-hydroxy-4-[(Z)-2-(4-hydroxyphenyl) vinyl]-2,3-dihydrobenzofuran-2-yl]benzene-1,2-diol, Procyanidin Dimer B7, Procyanidin B1, and Vitamin E had the highest binding affinity towards the three targeted proteins.* ***Conclusion:*** *These substances could make a good candidate for the management and suppression of cancer because they are effective against the proteins implicated in cancer development. To support these findings, in vitro study is still needed.*

***Author for Correspondence**
Alan S Mathew
E-mail: alansmathew11@gmail.com

Student, Department of Life Science, Kristu Jayanti College (Autonomous), Bengaluru, Karnataka, India

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INTRODUCTION

Cancer can result from the body's cells growing out of control [1–3]. Worldwide, and in nations of all financial levels, cancer is the leading cause of death. As populations expand, get older, and embrace riskier lifestyle choices, the number of

cancer diagnoses and deaths is predicted to climb dramatically, adding to the burden already present [1]. In the world, colorectal cancer (also known as colon cancer) is the third most prevalent cancer and the fourth most common cancer mortality cause, resulting in about 500,000 new cases and 600,000 deaths annually [2]. The colon and rectum, which start at the ileocecal valve at the very end of the small intestine and conclude at the anus, are the last part of the human digestive system. They are about one yard long and connect the ileocecal valve to the anus. Every five days, the stem cell population located at the base of the colonic epithelial cell crypts regenerates into new colonic epithelial cells, which line the organ's lumen. These cells are the source of colon cancers [3]. A crucial component of colorectal cancer's underlying structure is genomic instability [4]. Chromosome instability, which results in multiple alterations in chromosomal copy number and shape, is the most prevalent kind of genomic instability in colon cancer [5].

The PI3K, Akt, and mTOR pathways are activated in the majority of human malignancies [6]. A wide range of cellular processes, including survival, proliferation, metabolism, growth, angiogenesis, metabolism, metastasis, cell size, and motility are regulated by the phosphatidylinositol 3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) signaling pathway, which is hyperactivated or altered in many cancer types [7, 8]. The PI3K/AKT pathway can be activated in tumor cells to enhance VEGF secretion through both HIF-1 dependent and independent methods [6]. Transmembrane tyrosine kinase growth factor receptors, including those of the ErbB family, insulin-like growth factor 1 receptor (IGF-1R), fibroblast growth factor receptors (FGFR), and others, can activate the PI3K/AKT/mTOR pathway [9].

The primary coordinators of intracellular signaling in response to external stimulators are phosphatidylinositol 3-kinases (PI3Ks) [10]. In general, tiny Ras-related GTPases, heterotrimeric G proteins, and receptor-coupled tyrosine kinase activity can all activate PI3Ks [11]. Various oncogenes and growth factor receptors, including the insulin receptor tyrosine kinase (InsR), the related insulin-like growth factor 1 receptor (IGF-1R), epidermal growth factor (EGF), and platelet-derived growth factor receptors (PDGF-R), stimulate this signaling pathway [10]. PI3K is divided into the I, II, and III classes. Heterodimeric Class I PI3Ks are made of the combination of the regulatory and catalytic subunits [6]. Class I PI3Ks are further subdivided into class IA and class IB enzymes based on the differences in the regulatory subunits. Class IA is composed of three catalytic subunits (p110, p110, and p110), which are produced by the genes PIK3CA, PIK3CB, and PIK3CD. Together with these three catalytic subunits, five different p85-like regulatory subunits (p85, p85, p50, p55, and p55), encoded by the genes PIK3R1, PIK3R2, and PIK3R3, activate and associate with class IA. The p85 regulatory subunit, which facilitates binding to p110, has two Src homology 2 domains, nSH2 and cSH2. The inhibitory nSH2/cSH2 connections are lost after PI3K is activated downstream of phosphorylated receptors and their adaptors, which leads to PI3K activation [12]. The most frequently altered kinase in the human genome is encoded by the PIK3CA gene, which also codes for the p110a catalytic subunit of PI3K [13]. Catalytic subunit p110 of class IB is made up of p84 (PIK3R5) or p101 (PIK3R6) regulatory subunits, and it is encoded by the PIK3CG gene. Class I PI3Ks are brought to the plasma membrane by receptor tyrosine kinase (RTK) or GPCR activation, where they relieve p110 of its p85-mediated inhibition and directly phosphorylate PI(4,5)P2 to create PI(3,4,5)P3. Thus, this lipid functions as a second messenger, activating signaling proteins that are confined to the membrane and are essential for cell growth and survival, like AKT [12]. Protein kinase B (PKB), often known as Akt, is a 57-kDa serine/threonine kinase that plays a crucial component in the PI3K signaling cascade [14]. AKT1 (PKB-), AKT2 (PKB-), and AKT3 (PKB-) are the three AKT isoforms found in humans. They all have a similar structure and activation mechanism. AKT's N-terminal pleckstrin homology (PH) domain interacts with membrane lipids to help upstream kinases recognize it and move it to the membrane [15]. The movement of Akt from the cytoplasm to the inner surface of the cell membrane is crucial for the process of phosphorylation. Phosphatidylinositol-3,4,5-trisphosphate (PIP3) is a

phospholipid produced by PI3K that binds to the PH domain of Akt to cause it to be recruited to the membrane [14]. A number of downstream protein substrates, such as GSK3b, the Bcl-2-associated death promoter, forkhead in rhabdomyosarcoma, and the mouse double minute 2 homolog, are phosphorylated by Akt after it has been activated by phosphorylation on Thr308 or Ser473 [16]. 3-phosphoinositide-dependent protein kinases (PDKs) mediate Akt phosphorylation in the traditional manner. Once activated, Akt controls the activity of numerous downstream proteins involved in cellular metabolism, angiogenesis, migration, proliferation, and survival. In the PI3K/Akt/mTOR signalling pathway, the Akt is a well-studied effector of phosphoinositide 3-kinase (PI3K), and its dysregulation is a major factor in the etiology of many human malignancies [14]. Because phosphorylated AKT (pAKT) creates signals that disrupt typical regulatory mechanisms activating mTOR, it has been linked to the dysregulation of apoptosis, proliferation, and cell motility [16]. The mTOR gene is found on chromosome 1, and it is a 288.892 kDa serine/threonine protein kinase that has 2550 amino acids (including stop codons) and is encoded by 7650 nucleotides [17]. mTOR has crucial functions in a variety of biological processes, including cell proliferation, survival, autophagy, metabolism, and immunology. Numerous pathophysiological disorders including diabetes, aging, obesity, Alzheimer's disease and cancer, are influenced by the deregulated activity of mTOR. Through a number of pathways, including the stimulation of growth factor receptor signaling, glyolytic metabolism, angiogenesis, cancer cell migration, lipid metabolism and the repression of autophagy, upregulation of mTOR signaling can accelerate tumor growth and progression [18].

METHODS

Retrieval of Ligands

Indian Medicinal Plants, Phytochemistry and Therapeutics 2.0 (IMPPAT 2.0), Regardless of the plant parts, a total of 203 phytochemicals from the Vitis vinifera were chosen using a manually curated database that was created by digitizing information from more than 100 books on traditional Indian medicine, 7000+ published research articles, and other existing resources [19, 20]. The PubChem CID, canonical SMILES and the two-dimensional structures of the same were obtained from the PubChem Database [21].

Protein Retrieval and Purification

The phosphatidylinositol 3-kinase (PI3K), protein kinase B (AKT), and mammalian target of rapamycin (mTOR) target proteins' three-dimensional crystal structures were downloaded in PDB format from the Research Collaboratory for Structural Bioinformatics Protein Data Bank (RCSB PDB) at (https://www.rcsb.org/). The protein was prepared for docking investigation with the help of DS BIOVIA Discovery Studio. The receptor was prepared with polar hydrogen, and using the Discovery Studio program, the water molecule was taken out of the crystallized 3D structure of the receptor before it was saved as a PDB file [22].

Validation of Protein Structure

The Ramachandran plot is used to assess the quality of a protein based on the torsion angles (Psi and Phi) in a protein structure. Ramachandran plot statistics show how many amino acid residues were identified in the favorable, allowed, and disallowed regions. The hydrophobicity or hydrophilicity of the amino acids in a protein is measured using a hydrophilicity plot. The saved purified proteins files were used to obtain the Ramachandran plot and secondary structure of a protein using PDB sum generate and hydrophobicity chart from BIOVIA discovery Studio software.

Molecular Docking

In this research, the primary investigative method used is Molecular Docking. PyRx is a virtual screening application that may be used in computational drug development to test chemical libraries against potential therapeutic targets. The molecular docking of the 203 screened ligands was performed using the PyRx software's Molecular docking engine.

The ligands were docked with target proteins independently using PyRx software. Purified proteins were uploaded into PyRx as a macromolecule, and plant phytocompounds were added as ligands. Energy minimization was performed by applying the universal force field and the loaded ligands were converted into. pbqt format. The following grids were generated for each target protein, Akt (Center X:22.9039 Y:-10.241 Z:20.4812; and Dimensions(angstrom) X:33.1866 Y:51.1982 Z:56.8728), PI3K (Center X:35.8163 Y:46.9946 Z:26.7830; and Dimensions(angstrom) X: 97.2347 Y:72.2247 Z:70.7189), mTOR (Center X:61.4623 Y: -25.862 Z:6.9525; and Dimensions(angstrom) X:50.1889 Y:45.9108 Z:69.1252), The ligands were docked with the target proteins and the corresponding docking interactions were evaluated based on the binding affinity. In PyRx the ligands take 9 different conformational changes to attain the best binding scores. The binding affinity corresponding to zero RMSD (Root Mean Square Deviation) values was appraised as the best docking conformation as they demonstrate the least binding scores among all the conformations. As the ideal binding complex for each target protein, the top three conformations with the lowest binding affinity were chosen. The docked ligand structures were extracted as PDB files and the interaction was visualized in DS BIOVIA Discovery Studio.

Visualisation

The output (docked structures) from PyRx was visualized using the structure visualization tool BIOVIA discovery studio software. The best-binding conformations were retrieved in .pdb format and viewed with BIOVIA Discovery Studio Visualizer. The non-bond interactions and the two-dimensional and three-dimensional models were investigated.

Physiochemical Studies (ADMET Screening)

The ADMET analysis facilitates the process of drug discovery by evaluating the attributes such as physiochemical properties, medicinal chemistry, absorption, distribution, and toxicity ADMET properties are fundamental in identifying drug-likeness properties and determining pharmacological efficacy as a possible candidate for medicinal development. ADMET analysis was performed using SWISS ADME, an online server [20]. From the docking results, the ligands with the best binding affinity were selected for ADMET analysis. The canonical SMILES of the top six ligands were retrieved from PubChem and were subjected to ADMET evaluation in the SWISS ADME webserver.

RESULT

Ramachandran Plot Statistics

Protein kinase B (Akt protein), phosphatidylinositol 3-kinase (PI3K protein), and mammalian target of rapamycin (mTOR protein) Ramachandran maps were created using PDBsum Generate; as shown in Figure 1(d), Figure 2(c) and Figure 3(d) respectively.

Protein Kinase B (Akt Protein)

The purified structure of Akt Protein has 96.2% of its residues in the most favoured regions, 3.8% in additionally allowed regions, 0.0% in generously allowed regions and 0.0% in areas of the Ramachandran plot that are forbidden.

Phosphatidylinositol 3-kinase (PI3K Protein)

The purified PI3K protein's Ramachandran plot statistics revealed that 88.5% of the residues are in the most advantageous regions, 10.7% are in further permitted regions, 0.8% are in generously permitted regions, and 0.6% are in forbidden regions.

Mammalian Target of Rapamycin (mTOR protein)

In the purified structure of the mTOR Protein, 93.4% of the residues are located in the plot's most favored regions, 6.6% in additional permitted regions, 0% within generously allowed regions, and 0.0% in disallowed regions.

Secondary Structure

PDBsum Generate was used to examine the secondary structure of the three proteins namely, Akt Protein, PI3K Protein and mTOR Protein as depicted in Figure 1(b), Figure 2(a) and Figure 3(b) respectively.

Protein Kinase B (Akt Protein)

The Akt Protein predicted secondary structure includes 1 sheets, 2 beta hairpins, 1 beta bulge, 3 strands, 13 helices, 18 helix-helix interacs, 18 beta turns and 4 gamma turns. The structure contains 217 residues in total.

Phosphatidylinositol 3-kinase (PI3K Protein)

The PDBsum results for this PI3K Protein secondary structure prediction are 5 sheets, 10 beta hairpins, 10 beta bulges, 24 strands, 39 helices, 72 helix-helix interacs, 42 beta turns and 13 gamma turns. The structure comprises 872 residues in total.

Mammalian Target of Rapamycin (mTOR Protein)

In the case of mTOR Protein, the depicted PDBsum results are 2 sheets, 3 beta hairpins, 2 beta bulges, 6 strands, 8 helices, 7 helix-helix interacs, 12 beta turns and 3 gamma turns. The structure constitutes 211 residues in total.

Hydrophobicity Plot

The DS BIOVIA Discovery Studio software was used to create and analyze the hydrophobicity plots for the Akt Protein, PI3K Protein, and mTOR Protein, as shown in Figure 1(c), Figure 2(d), and Figure 3(a).

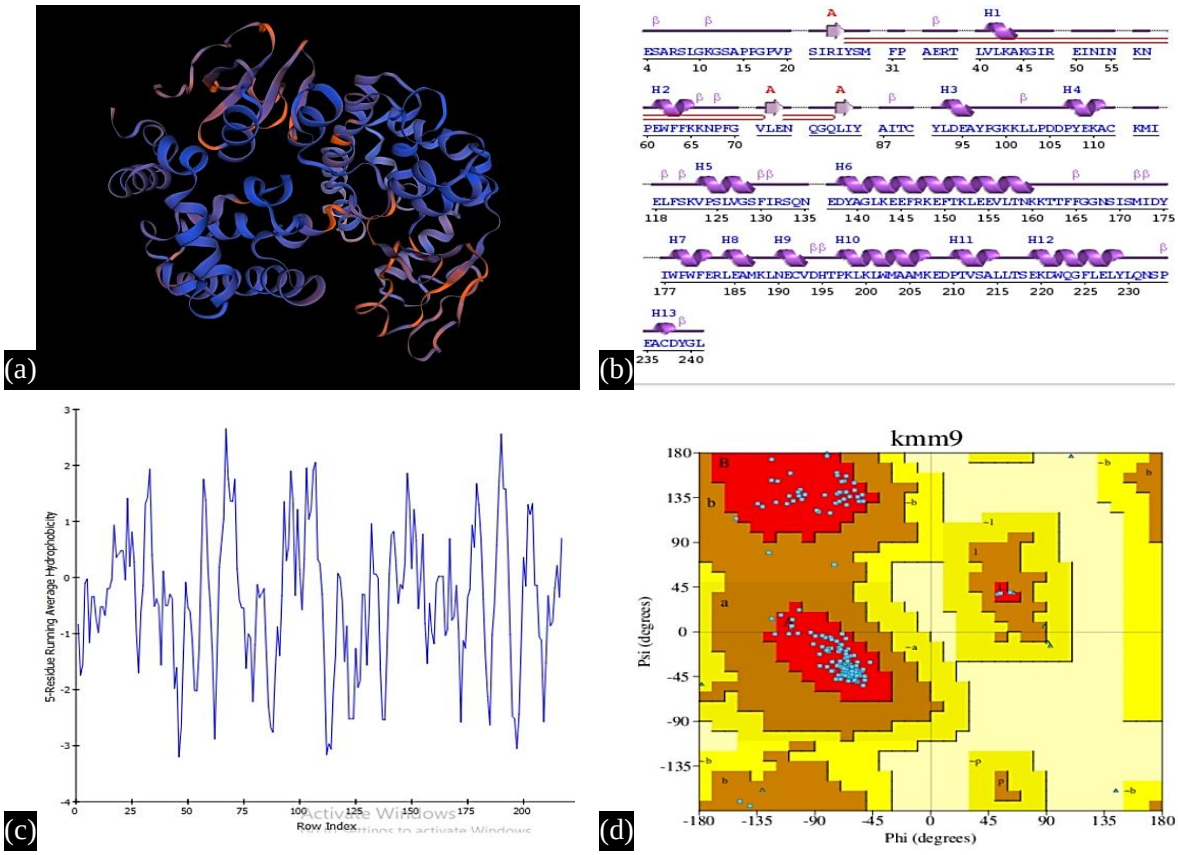


Figure 1. Structural analysis of protein kinase b (akt protein), (a) purified akt protein structure, (b) secondary protein structure, (c) hydrophobicity plot and (d) ramachandran plot.

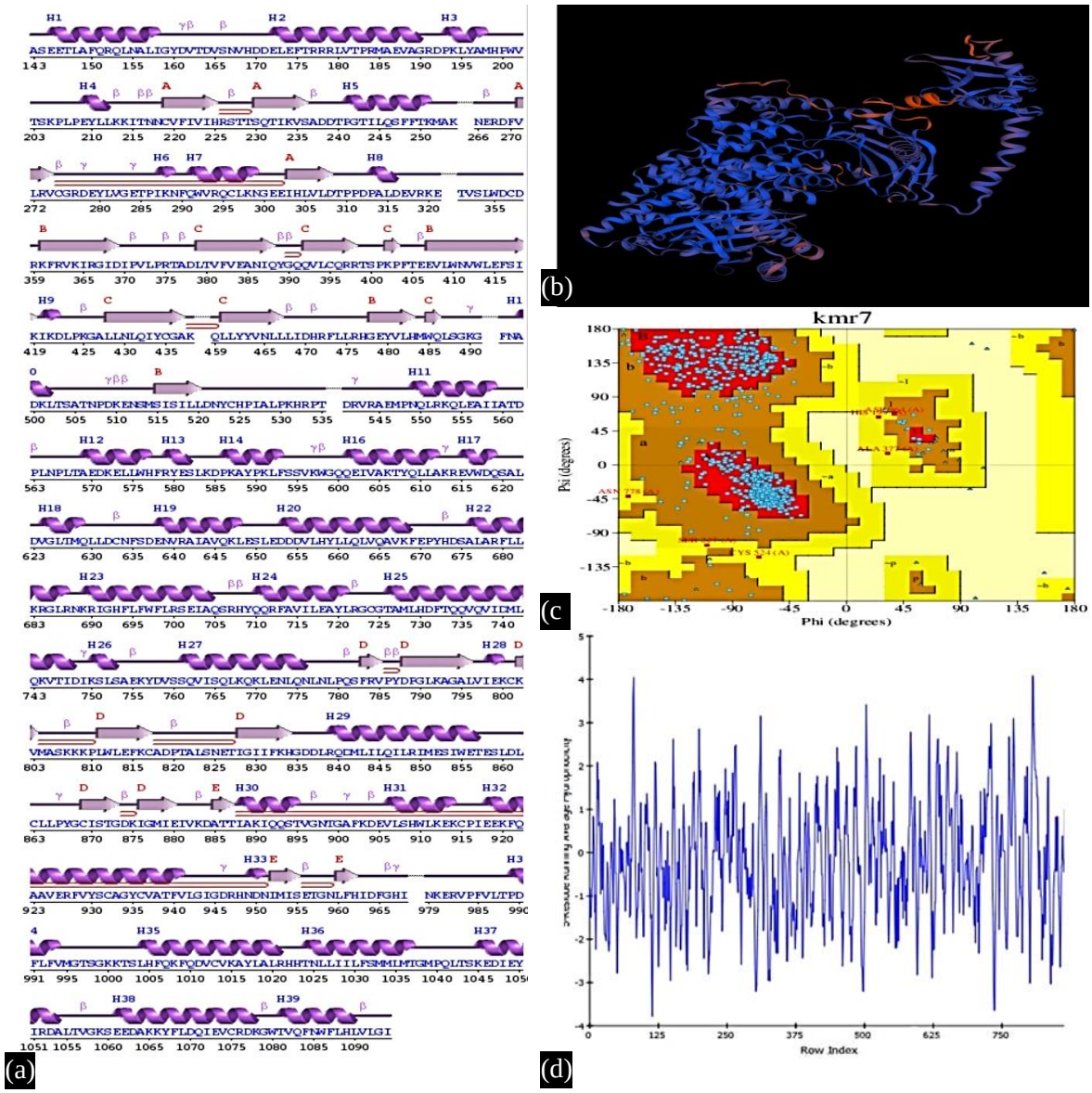
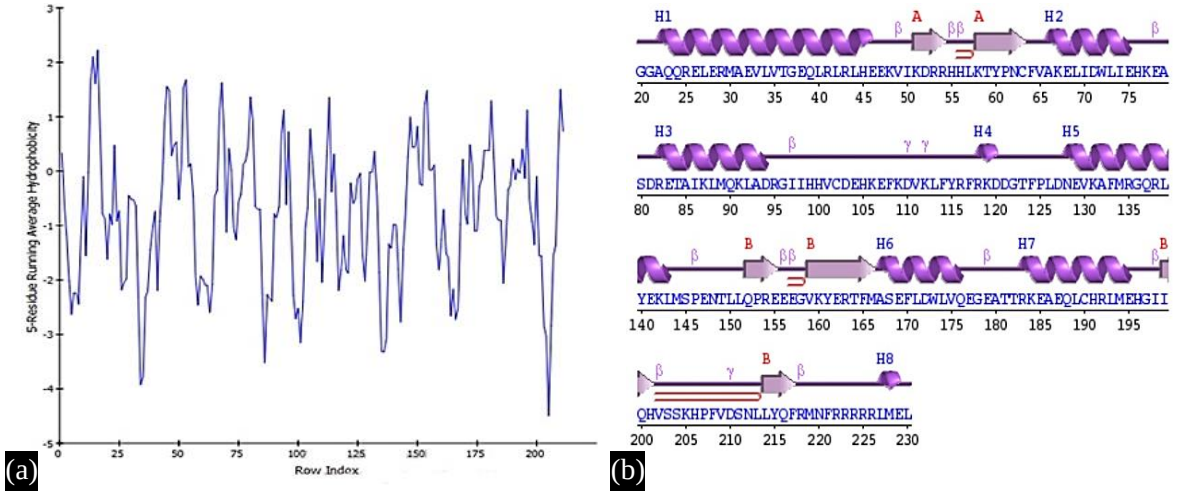


Figure 2. Structural Analysis of phosphatidylinositol 3-kinase (PI3K protein); (a) Secondary protein structure, (b) Purified PI3K protein structure, (c) Ramachandran Plot and (d) Hydrophobicity plot.



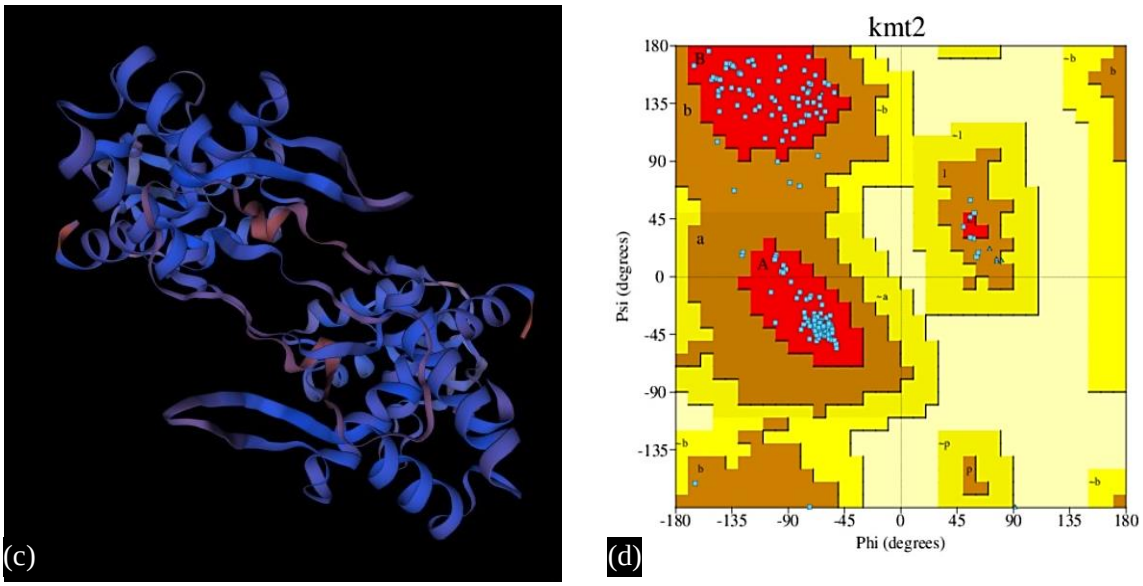


Figure 3. Structural Analysis of mammalian target of rapamycin (mTOR protein); (a) Hydrophobicity plot (b) Secondary protein structure, (c) Purified mTOR protein structure and (d) Ramachandran plot.

MOLECULAR DOCKING

In this study, a total of 203 ligands were docked against three target proteins of *Vitis vinifera:* Akt Protein, PI3K Protein, mTOR Protein using PyRx. The optimal binding complex for every targeted protein was determined after docking, and it was the conformation having least binding affinity and 0 RMSD value.

The top three ligands with the lowest binding affinity were selected or each protein namely Protein kinase B(Akt protein) (Table 1), Phosphatidylinositol 3-kinase(PI3K protein) (Table 2) and Mammalian target of rapamycin(mTOR protein) (Table 3).

Table 1. Binding affinity of the top three ligands with Akt Protein.

Ligand	Binding Affinity
Lupeol	-11.7
4-[(2R,3R)-3-(3,5-dihydroxyphenyl)-6-hydroxy-4-[(Z)-2-(4-hydroxyphenyl)vinyl]-2,3-dihydrobenzofuran-2-yl]benzene-1,2-diol	-10.3
Procyanidin dimer B7	-10.0

Table 2. Binding affinity of the top three ligands with PI3K Protein.

Ligand	Binding Affinity
Lupeol	-11.5
4-[(2R,3R)-3-(3,5-dihydroxyphenyl)-6-hydroxy-4-[(Z)-2-(4-hydroxyphenyl)vinyl]-2,3-dihydrobenzofuran-2-yl]benzene-1,2-diol	-10.4
Procyanidin B1	-9.5

Table 3. Binding affinity of the top three ligands with mTOR Protein.

Ligands	Binding Affinity
Lupeol	-12.3
4-[(2R,3R)-3-(3,5-dihydroxyphenyl)-6-hydroxy-4-[(Z)-2-(4-hydroxyphenyl)vinyl]-2,3-dihydrobenzofuran-2-yl]benzene-1,2-diol	-10.3
Vitamin E	-9.9

VISUALIZATION

The selected ligands were then visualized using DS BIOVIA Discovery Studio software. The 3D and 2D models of the same were generated. Moreover, the interactions of the ligands with amino acids in the protein's binding pocket were analysed. Visualization of Akt Protein, PI3K Protein and mTOR Protein is given in Figures 4, 5 & 6 respectively.

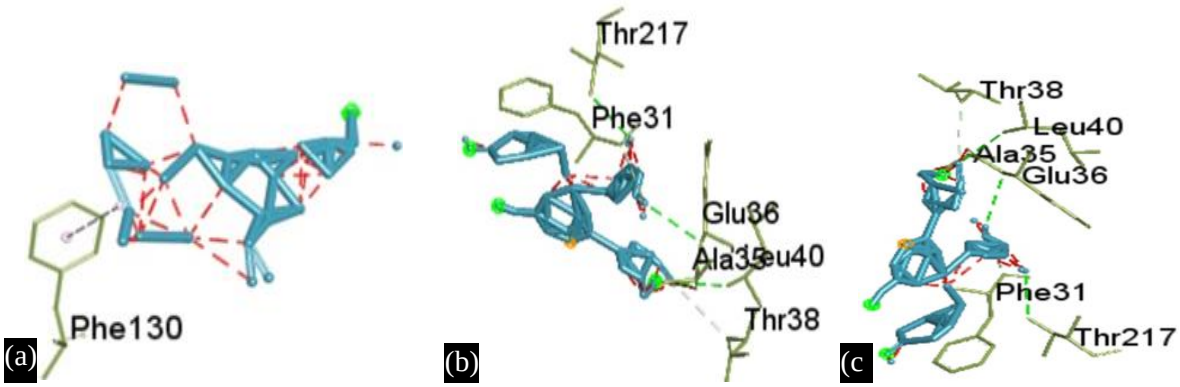


Figure 4. Interactions of top ligands with Akt Protein, (a) 259846, (b) 5279245, (c) 131752345

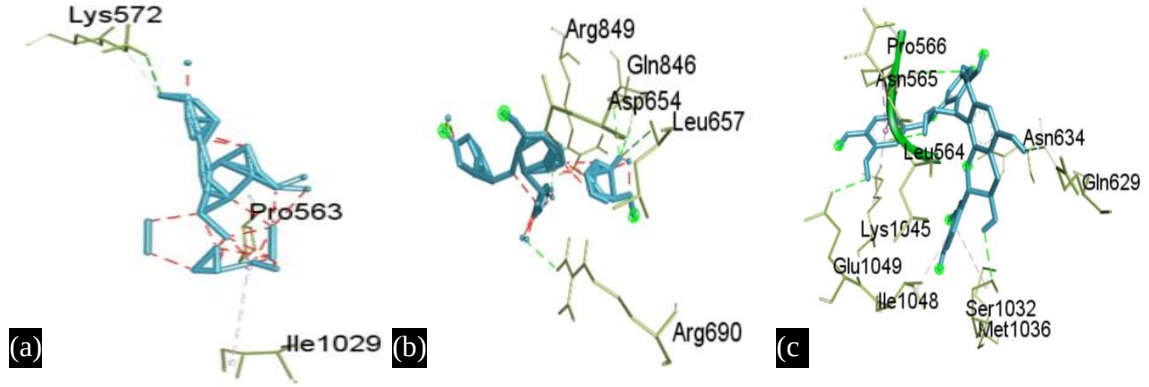


Figure 5. Interactions of top ligands with PI3K Protein, (a) 259846, (b) 5279245, (c) 11250133.

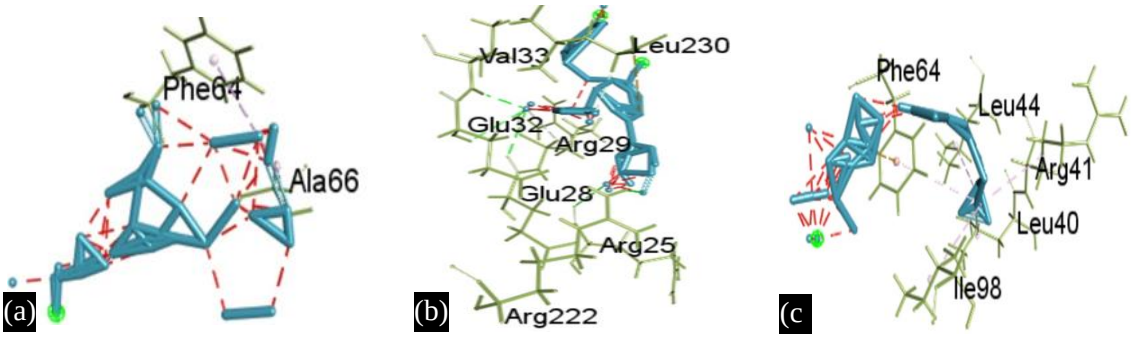


Figure 6. Interactions of top ligands with mTOR Protein, (a) 259846, (b) 5279245, (c) 14985

ADMET Analysis

With the aid of ADMET Lab 2.0, 5 ligands namely Lupeol (PubChem CID: 259846), 4-[(2R,3R)-3-(3,5-dihydroxyphenyl)-6-hydroxy-4-[(Z)-2-(4-hydroxyphenyl)vinyl]-2,3 dihydrobenzofuran-2-yl]benzene-1,2-diol (PubChem CID: 5279245), Procyanidin dimer B7 (PubChem CID: 131752345), Procyanidin B1 (PubChem CID: 11250133), Vitamin E (PubChem CID: 14985) were examined for their physiochemical properties (Table 4), medicinal chemistry (Table 5), absorption (Table 6), distribution (Table 7), metabolism (Table 8), and toxicity (Table 9).

Table 4. Physiochemical Properties of the top derivatives of Vitis vinifera.

PubChem ID	MW	Vol	nHA	nHD	nRot	nRing	nHet	fChar	Flex	TPSA	LogS
259846	426.390	490.807	1	1	0	5	1	0	0.038	20.230	-6.199
5279245	470.140	77.319	7	6	4	5	7	0	0.138	130.610	-3.496
131752345	578.140	549.942	12	10	3	6	12	0	0.088	220.760	-3.876
11250133	578.140	549.942	12	10	3	6	12	0	0.088	220.760	-3.968
14985	430.380	502.698	2	1	12	2	2	0	1.091	29.460	-6.500

MW: *Molecular weight;* ***Vol:*** *Volume;* ***nHA:*** *Number of hydrogen bond acceptors;* ***nHD:*** *Number of hydrogen bond donors;* ***nRot:*** *Number of rotatable bonds;* ***nRing:*** *Number of rings;* ***nHet:*** *Number of heteroatoms;* ***fChar:*** *Formal charge;* ***Flex:*** *Flexibility;* ***TPSA:*** *Topological Polar Surface Area;* ***LogS:*** *Log of the aqueous solubility.*

Table 5. Medicinal Properties of the top derivatives of Vitis vinifera.

PubChem ID	QED	PAINS	Lipinski	Fsp3	SA Score
259846	0.421	0	Accepted	0.933	4.663
5279245	0.175	1	Accepted	0.071	3.642
131752345	0.158	1	Rejected	0.200	4.642
11250133	0.159	1	Rejected	0.200	4.519
14985	0.359	0	Accepted	0.793	3.780

QED: *Quantitative estimate of drug-likeness;* ***PAINS:*** *Pan Assay Interference Compounds;* ***Fsp3:*** *Number of sp3 hybridized carbons/total carbon count;* ***SA Score:*** *Synthetic Accessibility Score.*

Table 6. Absorption properties of the top derivatives of Vitis vinifera.

PubChem ID	Caco-2	MDCK	Pgp-inh	Pgp-sub	HIA	F(20%)
259846	-5.020	7.8e-06	--	---	---	-
5279245	-5.911	7.2e-06	+	---	--	+++
131752345	-60649	4.1e-06	---	---	+++	+++
11250133	-6.774	4.3e-06	---	---	+++	+++
14985	-4.776	7.1e-06	---	---	---	+++

Caco-2: *Caco-2 permeability;* ***MDCK:*** *MDCK (Madin-Darby canine kidney) permeability;* ***Pgp-inh:*** *Pgp-inhibitor;* ***Pgp-sub:*** *Pgp-substrate;* ***HIA:*** *Human Intestinal Absorption;* ***F(20%):****20% Bioavailability.*

Table 7. Distribution Properties of the top derivatives of Vitis vinifera.

PubChem ID	BBB	PPB	VD	Fu
259846	++	98.802%	1.731	2.211%
5279245	---	97.836%	0.670	2.496%
131752345	---	90.344%	0.456	8.479%
11250133	---	88.707%	0.436	7.875%
14985	++	101.236	6.837	1.988%

BBB: *Blood-Brain Barrier Penetration;* ***PPB:*** *Plasma Protein Binding;* ***VDss:*** *Volume Distribution;* ***Fu:*** *Fraction unbound in plasma*

Table 8. Metabolism and Excretion Properties of the top derivatives of Vitis vinifera.

PubChem ID	CYP1A2-inh	CYP1A2-sub	CYP3A4-inh	CYP3A4-sub	CL	T1/2
259846	---	+	--	+	17.929	0.010
5279245	+	--	++	--	13.880	0.751
131752345	---	--	---	--	7.903	0.675
11250133	---	--	---	-	13.419	0.612
14985	---	--	--	--	8.280	0.022

CL: *Clearance;* ***T1/2:*** *Half-life.*

Table 9. Toxicity Properties of the top derivatives of Vitis vinifera.

PubChem ID	hERG	H-HT	DILI	Ames	Carcinogenicity	Respiratory Toxicity	IGC50	$LC_{50}FM$
259846	---	--	---	---	---	++	5.481	6.821
5279245	--	--	---	-	---	---	5.331	6.236
131752345	---	---	-	-	---	---	4.948	6.403
11250133	---	---	+	--	---	---	4.896	6.500
14985	---	--	---	---	---	--	5.486	5.816

hERG: *The human Ether-à-go-go-Related Gene;* ***H-HT:*** *Human Hepatotoxicity;* ***DILI:*** *Drug Induced Liver Injury;* ***Ames:*** *The Ames Toxicity Test.*

DISCUSSION

Worldwide, and in nations of all financial levels, cancer is the leading cause of death. As populations age, grow older, and embrace risky lifestyle choices, the number of cancer diagnoses and deaths is anticipated to rise sharply, adding to the burden already present.[1] Colorectal cancers are the second and third most common cancers in both men and women, respectively. In 2012, 614,000 women and 746,000 men worldwide received a colorectal cancer diagnosis. The development of defining characteristics of cancer in colon epithelial cells is facilitated by environmental and genetic variables that cause colorectal cancer. The gradual accumulation of genetic mutations and epigenetic changes that activate oncogenes and inactivate tumour suppressor genes is one way these defining characteristics of cancer are acquired. Genomic and/or epigenomic stability has been reported to have been lost in the majority of early neoplastic lesions in the colon, including aberrant crypt foci, adenomas, and serrated polyps. A significant molecular and pathophysiological element in the emergence of colorectal cancer is most likely this loss. Loss of genomic and epigenomic stability accelerates the accumulation of mutations and epigenetic changes in tumor suppressor genes and oncogenes, which in turn fuels the malignant transformation of colon cells through cycles of clonal expansion that favor cells with the most aggressive and malignant traits [23].

Multiple aspects of cell growth and survival depend on the PI3K, Akt and mTOR signaling pathways in both pathological and healthy contexts. Due to their strong linkages, they are frequently regarded as a single, distinct route that interacts with a number of other pathways, including Ras, Notch, Wnt, Hypoxia Inducible Factors (HIFs), Mitogen-Activated Protein Kinase (MAPK), Notch, and Wnt. One of the major pathways responsible for medication resistance and promoting malignancy in patients with solid cancer is the PI3K-AKT-mTOR signaling. The PI3K-Akt pathway is emerging as a viable target for cancer and related illnesses, but only a small number of medications have been licensed so far, and side effects are its main drawback. [24]

Fruits and vegetables, which are members of the plant kingdom, are a rich source of phytochemicals with diverse chemical structures; many of them have already undergone significant research to see whether they may have anticancer or chemopreventive properties. Therefore, because fruits and vegetables are key sources of vitamins, minerals, and fiber, they are "more natural" than other methods of reducing cancer risk and don't have "any side effects" in addition to helping to maintain good overall health [25].

GSE reduces the growth of HT-29 cells both in vitro and when implanted as tumor xenografts in athymic nude mice, which is more significant because it stops the proliferation of these cancer cells. Animal models for colon cancer chemoprevention showed that grape seed proanthocyanidins significantly decreased the azoxymethane-induced colonic aberrant crypt foci, a precursor lesion for colon cancer in a rat dual-organ tumor model [25]. In colon cancer cell lines, grape seed extract (GSE) exhibited anticancer properties and triggered apoptosis. Different colorectal cancer cell lines (SW480, SW620, and HCT116) were selectively induced to undergo apoptosis by grape seed extract, which was accompanied by the release of cytochrome c into the cytoplasm of the cancer cells and the loss of

mitochondrial membrane potential. It's interesting to note that grape seed extract not only reduced mucositis caused by 5-fluorouracil in rats after chemotherapy, but also enhanced the anticancer effect of the drug in a dose-dependent manner in vitro. Its protective effect was more pronounced in the proximal jejunum than the distal small intestine [26].

In this study, the antibacterial effectiveness of 203 phytocompounds against Akt/PI3K/mTOR pathways was assessed. The ligands Lupeol, 4-[(2R,3R)-3-(3,5-dihydroxyphenyl)-6-hydroxy-4-[(Z)-2-(4-hydroxyphenyl)vinyl]-2,3-dihydrobenzofuran-2-yl]benzene-1,2-diol and Procyanidin dimer B7 had the lowest binding affinity against the targeted protein Akt and hence were selected for further visualization. Ligands namely Lupeol, 4-[(2R,3R)-3-(3,5-dihydroxyphenyl)-6-hydroxy-4-[(Z)-2-(4-hydroxyphenyl)vinyl]-2,3-dihydrobenzofuran-2-yl]benzene-1,2-diol and Procyanidin B1 had a higher binding affinity of -11.5, -10.4 and -9.5 respectively with PI3K protein were chosen. The ligands Lupeol, 4-[(2R,3R)-3-(3,5-dihydroxyphenyl)-6-hydroxy-4-[(Z)-2-(4-hydroxyphenyl)vinyl]-2,3-dihydrobenzofuran-2-yl]benzene-1,2-diol and Vitamin E were selected for mTOR based on their binding affinity score. BioVIA Discovery Studio from Dassault Systems was used to visualize these interactions.

The ADMET properties of the ligands were then assessed because it is crucial to understand the adsorption, distribution, metabolism, excretion, and toxicity characteristics of the medications. Using ADMET Lab 2.0, 5 substances were evaluated to determine their pharmacokinetic and therapeutic potential (Tables 6–9). In the course of the current inquiry, efforts have been undertaken to create pharmacological candidates that can prevent the growth of tumors. The grape plant's substantial phytochemical derivatives showed some encouraging protein target inhibitory activity. Thus, the current study opens a doorway into the research into prospective antibiotic replacement therapies.

CONCLUSION

The plant Vitis vinifera's numerous phytocompounds were examined in the current study, and the findings show that it has a significant potential as a therapeutic option, particularly for diseases associated to colorectal cancer. This study reveals that these plants have considerable promise for the development of phytomedicines due to their anticarcinogenic properties. According to this study, the ligand Lupeol followed by 4-[(2R,3R)-3-(3,5-dihydroxyphenyl)-6-hydroxy-4-[(Z)-2-(4-hydroxyphenyl)vinyl]-2,3-dihydrobenzofuran-2-yl]benzene-1,2-diol are the two compounds with best binding affinity for the proteins phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT)/mammalian target of rapamycin (mTOR). In vitro methods can be used to learn more about these substances.

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Abbreviations

PI3K: phosphatidylinositol 3-kinase
mTOR*:* mammalian target of rapamycin

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