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RESEARCH ARTICLE

Assessing the Mechanism of Multiple Targets of Grape Seed for Psoriasis Disorder Via Network Pharmacology, Molecular Docking and Dynamics

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Abstract

Background: This study targeted to explore the therapeutic targets and mechanism of grape seed components in treating psoriasis using network pharmacology, molecular docking, and dynamic simulations. **Aim:** Grape seed extract was subjected *in silico* studies to find the importance of its bioactives to alleviate psoriasis symptoms. **Methods:** STRING examined protein-protein interactions. Shiny GO performed gene ontology, and KEGG enrichment analysis. The network diagram depicting the Grape seed constituents-target-Psoriasis pathway was generated using Cytoscape 3.10.0. The Schrodinger software was used to perform molecular docking and dynamic simulations. **Results:** Grape seed constituents and Psoriasis had 232 common targets, and Grape seed constituents could affect the underlying procedures that trigger cell death and the proliferation of cells in psoriasis. Molecular docking and dynamic simulations showed that Grape seed constituents Epicatechin-3-gallate, Procyanidin b4, b6 had the best docking and binding with the core targets of Psoriasis, such as HSP90AA1 and AKT1. **Conclusion:** Grape seed constituents could regulate PI3K-AKT and Th17 signaling pathways and inhibit inflammation and proliferative factors involved in Psoriasis.

Major Findings: The bioactives like Proanthocyanidins and epicatechin identified in grape seed extract were regulating inflammatory, immunomodulatory pathways by targeting genes like HSP90AA1 and AKT1, showing promising anti psoriatic properties.

Keywords: Grape Seed, Molecular Docking, Network Pharmacology, Psoriasis, Pathway Analysis

1. Introduction

Psoriasis is a chronic dermatological disorder marked by skin cell inflammation and aberrant proliferation. This phenomenon has a significant impact on a considerable number of individuals globally and has garnered heightened interest from researchers and medical experts[1]. Research on the frequency of psoriasis in adults has provided inconsistent findings (0.51% to 11.43%), and among children (0% to 1.37%)[2]. The probability of psoriasis changes over time, differ based on age and gender. Interestingly psoriasis tends to develop in two age peaks; the first peak typically occurs between the ages of 30 to 39 while the second peak is seen between 60 to 69 years[3]. Psoriasis is widely acknowledged as a concern, for health[1]. It involves interactions between factors such as genetics, immune system functioning and environmental influences[4,5]. Researchers have identified predisposition, immune dysregulation and exposure to triggers as contributors to the development of psoriasis. Preventing and treating psoriasis is possible, early intervention is essential in order to reduce the psychological impact on individuals[4,5]. Through effective management, we can significantly enhance the quality of life for individuals impacted by psoriasis. Establishing treatment strategies that target the underlying mechanisms of this condition alongside approaches are vital, in achieving successful outcomes[6]. The complexity of psoriasis and the need

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for effective therapeutic interventions highlight the significance of understanding the specific molecular pathways and factors contributing to the condition[7]. Overall, psoriasis is a significant dermatological disorder with global impact and addressing its epidemiological and pathological aspects is imperative for early intervention and improved patient outcomes.

Grape seeds (*Vitis vinifera)* is rich in proanthocyanidins, which are polyphenolic compounds known for their antioxidant and anti-inflammatory properties and inhibit the proliferation and differentiation of keratinocytes, which are the main cells in the epidermis[8]. The current research used network pharmacology and core molecular docking tools to predict and analyse potential pharmacological strategy for grape seed constituents for the management of psoriasis, and to provide the basis for future investigational research. The whole study approach of this work is shown in graphical abstract.

2. Materials and Methods

2.1 Bioactive Mining

Information was gathered, on the bioactive compounds found in Grape seed from literature sources and accessing that can be readily retrieved, such as Dr. Duke's ethnobotanical database on small molecules[9]. These bioactives were then evaluated for their suitability as drugs using the Schrödinger QikProp module, which estimates ADME parameters. This screening process takes into account factors such, as solubility, permeability and toxicity to identify drug candidates among the bioactives found in grape seeds.

2.2 Prediction of Grape Seed Bioactive Targets

The two-dimensional structures of the components of Grape seed are gathered from the PubChem database[10], the active component targets were projected using methods of prediction, the Swiss Target Prediction database[11] and PharmMapper Server[12]. The predicted targets were included in the UniProt Resource Library[13], implemented a filter that included all desired targets for the species as Homo sapiens and integrated the targets in DisGeNET[14] to create the potential Psoriasis target library.

2.3 Psoriasis-Related Target Retrieval and Screening

Psoriasis-related therapeutic targets were searched in databases like DisGeNET, OMIM[15] and GeneCards[16] via the use of the keyword "Psoriasis," a registry for putative therapeutic targets for psoriasis was established.

2.4 Predicting Targets and Constructing the PPI Network for Grape Seed Bioactives on Psoriasis

The common targets between Grape seed bioactives prediction and Psoriasis screening were generated through Venn diagram using Bioinformatics genomics database[17]. A Protein-Protein Interaction (PPI) network diagram was generated using the STRING 12.0 database[18] to illustrate the common targets of grape seed bioactives and psoriasis assuming the species is "Homo sapiens" and the minimum interaction threshold is set at Medium Confidence (>0.4). To investigate the PPI network's structure, the "Network Analyzer" plug-in was used in the Cytoscape 3.6.0 program. A high Degree, the primary topological indication, was used to choose the important targets of the components of grape seeds[19].

2.5 Hub Proteins Identification using Cytohubba and Mcode Analysis

Discovering hub targets was accomplished using the Cytohubba extension, version 3.6.0, in Cytoscape from PPI network by selecting MCC option, top 20 targets were listed out, later the PPI network was analysed for the presence of clusters by using MCODE analysis where 8 clusters were identified, the first cluster has all the hub proteins that obtained by using Cytohubba plugin so this cluster was selected as it represents the potential biomarkers involved in psoriasis[20].

2.6 Grape Seed Constituent go Enrichment Analysis and Exploring Enrichment Pathways from the Kegg Database

Targets that are common include grape seed constituents alongside psoriasis were brought into the Shiny GO database[21], using a 0.05 FDR criterion, the biological species was classified as Homo sapiens. After performing enrichment analysis on the GO and KEGG pathways, the data was examined. Important pathways were mapped out using network diagrams, KEGG and GO enrichment diagrams were produced. Which identified

the 20 targets with the highest Degree. With the help of Cytoscape 3.6.0, examined the Grape seed bioactives-Target-Psoriasis-Pathway network's structure.

2.7 Molecular Docking of Selected Hub Proteins

Preparation of proteins and generation of receptor grids in order to find the target gene's protein structure, the PDB[22] database was searched. The procedure for preparing the protein was carried out employing protein preparation wizard of Schrodinger suite. This docking study used the GLIDE (Grid-based Ligand Docking with Energetics) tool to find the best possible interactions between the ligand and the protein. In order to identify the spot where the co-crystallized ligand was located, the Receptor grid generation tool was used. In order to get more precise scores for ligand poses, this grid specific the precise properties and shape of the targeted protein[11,23]. Schrodinger software was used to calculate the docking score and to envisage the docked molecule that has the best score.

2.7.1 Setting up the Ligand Collection

A total of 37 compounds drawn from the Pub Chem chemical library were used in the docking analysis. The energy-minimizing three-dimensional structures of the compounds at a pH of 7 ± 2 were constructed using the Ligprep module of the Schrödinger suite. Using Schrödinger's QikProp module, the conformers' ADME parameters were predicted.

2.7.2 Docking of proteins with ligands

Standard Precision (SP) docking was performed for the selected core hub proteins with the ligands based on the connection of protein with the ligand that observed in the network of Grape seed bioactives-Target-Psoriasis-Pathway network[12,24].

2.7.3 The Prediction of Toxicity and Pharmacokinetics

The selected phytoconstituents ADME characteristics were predicted using the QikProp module[24]. Using this module, one may examine pharmacokinetic characteristics and attributes such as Molecular weight of the molecule (mol_MW), Estimated number of hydrogen bonds that would be accepted by the solute from water molecules in an aqueous solution (accptHB), Predicted brain/blood partition coefficient (QPlogBB), Predicted skin permeability (QPlogKp), Human Oral Absorption-Predicted qualitative human oral absorption (log Kp), Rule Of Three- Number of violations of Jorgensen's rule of three. The three rules are: Predicted aqueous solubility, predicted apparent Caco-2 cell, Primary Metabolites < 7., Lipinski's rule of five. The rules are molecular weight < 500, Predicted octanol/water partition coefficient, donorHB ≤ 5, accptHB ≤ 10, compounds which meet these criteria were assessed for their drug-likeness[23].

2.8 Molecular Dynamics Simulation of the Components with Good Docking Score

Molecular Dynamic (MD) simulation studies were implemented by the Schrödinger molecular modelling tool Desmond 4.2 to understand the ligand-protein complex interaction in a simulated physiological solvent-based system. The three complexes that achieved the highest SP dock scores were subjected to molecular dynamic simulations, Procyanidin b4- EGFR, Procyanidin b6-AKT1, Procyanidin b4- HSP90AA1.

A Simple Point Charged (SPC) solvent model was used to build the docked complex system of ligand and protein, with an orthorhombic box measuring 10 ˚A on each side. By adding appropriate amounts of Na^+ and Cl^- ions, the built system was rendered neutral, the systems were solvated using TIP3P solvent model. The NPT ensemble conditions were used to run the simulation, which included the following parameters: period 100 ns, temperature 300 K, pressure 1 bar[23]. The 25 ps and 1000 frames recording intervals allowed the simulation to capture the trajectory[24]. For the ligand-protein complex that was chosen, the Root Mean Square Deviation RMSD was computed. A measure of the average displacement of the selected atoms inside a compound with respect to the reference trajectory frame is the Root Mean Square Deviation (RMSD), a Simulation Interaction Diagram (SID), was created for the purpose of analysing the trajectory.

3. Results

3.1 Prediction of Grape Seed Bioactive Targets

The predicted targets from Swiss Target Prediction, PharmMapper Server, were introduced.

3.1.1 Target Inspection for Psoriasis

Utilizing a combination of the Disgenet, GeneCards, along with Omim databases, 4728 Psoriasis targets were obtained, 232 common targets of Grape seed bioactives -Psoriasis data was collected using intersection, and the Venn diagram was made using Bioinformatics and evolutionary genomics database, displayed in (Figure 1a).

3.1.2 Constructing a Protein-Protein Interaction Network of Grape Seed Constituents on Psoriasis

The STRING database was queried for the overlapping targets in order to build the PPI network. The network was assessed using the Cytoscape 3.6.0 tool (Figure 1b). Twenty top targets have been identified from the PPI network as per their degree value, with the values shown in decreasing order, as shown in (Table 1) which were considered as the core targets of constituents related to grape seed.

3.2 Analysing Cytohubba and MCODE Data to Identify Hub Proteins

The MCC (Maximal Clique Centrality) algorithm, in the CytoHubba plugin (Table 2) was used to select the 20 hub genes from the PPI network. Molecular Complex Detection Clustering (MCODE) on the Psoriasis, nodes in the protein-protein interaction network was being

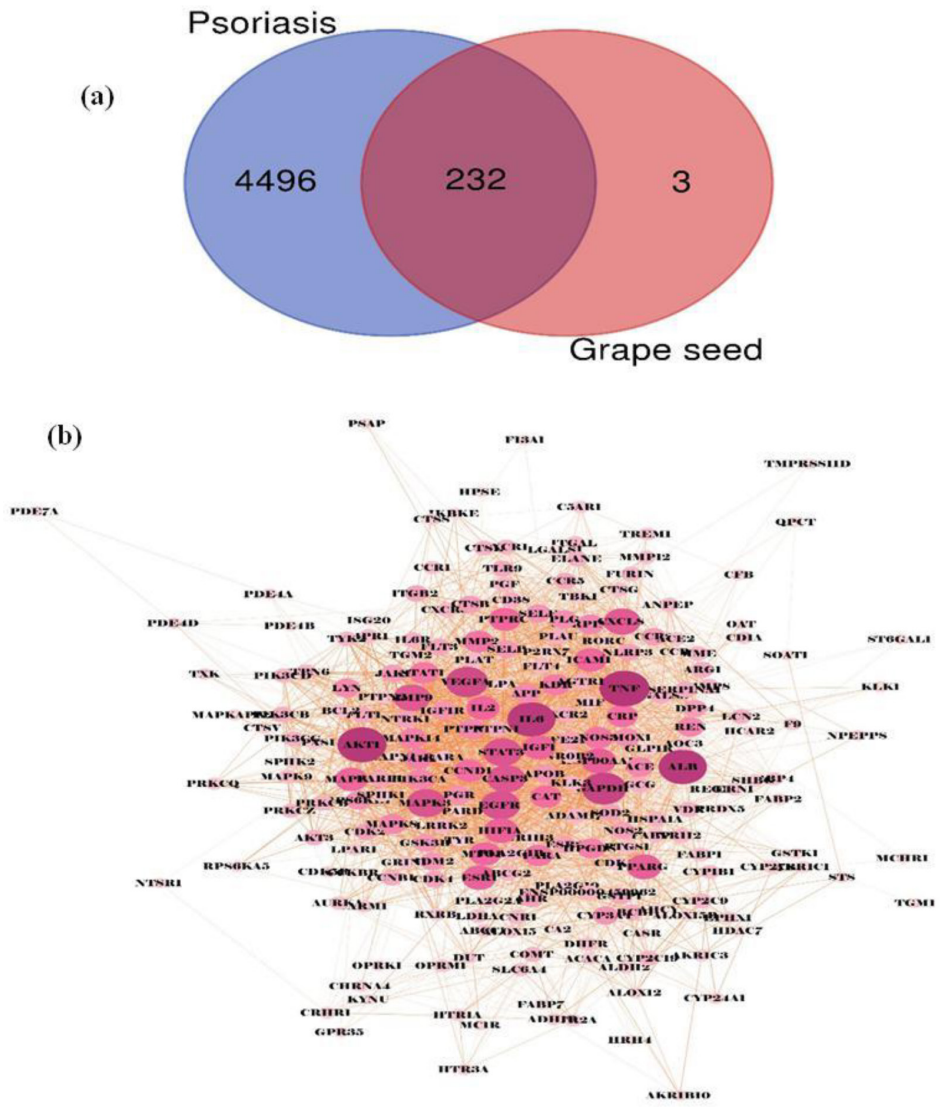


Figure 1. Common targets of psoriasis and grape seed constituents. **(a).** Venn diagram showing the overlap among Psoriasis targets (blue), Grape seed related targets (pink). **(b).** Protein-protein interaction network of the 232 common targets, based on degree - high degree big size dark colour and vice versa for low values.

Table 1. Top 20 proteins that obtained from String protein-protein interactions network based on degree as topological parameter

Protein	Name	Betweenness centrality	Closeness centrality	Degree
TNF	Tumor Necrosis Factor	0.076224379	0.71875	142
AKT1	AKT Serine/Threonine Kinase 1	0.071327842	0.714285714	139
ALB	Albumin	0.07180208	0.705521472	136
IL6	Interleukin 6	0.060256309	0.703363914	135
GAPDH	Glyceraldehyde-3-Phosphate Dehydrogenase	0.041675088	0.67251462	121
VEGFA	Vascular Endothelial Growth Factor A	0.027557718	0.651558074	112
EGFR	Epidermal Growth Factor Receptor	0.032841378	0.633608815	102
MAPK3	Mitogen-Activated Protein Kinase 3	0.025098816	0.623306233	100
STAT3	Signal Transducer and Activator Of Transcription 3	0.016801918	0.613333333	98
CASP3	Cysteine-ASPartic Protease 3	0.016442808	0.621621622	96
MMP9	Matrix Metallopeptidase 9	0.017332738	0.611702128	92
CXCL8	C-X-C Motif Chemokine Ligand 8	0.015345794	0.606860158	90
PPARG	Peroxisome Proliferator Activated Receptor Gamma	0.025105486	0.602094241	83
HSP90AA1	Heat Shock Protein 90 Alpha Family Class A Member 1	0.015924071	0.594315245	83
HIF1A	Hypoxia Inducible Factor 1 Subunit Alpha	0.009313141	0.586734694	81
ESR1	Estrogen Receptor 1	0.024521438	0.595854922	80
IGF1	Insulin Like Growth Factor 1	0.012433952	0.58974359	77
IL2	Interleukin 2	0.018017924	0.576441103	75
ICAM1	Intercellular Adhesion Molecule 1	0.006335337	0.572139303	74
MAPK1	Mitogen-Activated Protein Kinase 1	0.015285842	0.582278481	74

focused. We set the MCODE Score to be greater than or equal to 6 allowing us to identify the interconnected regions within the network. In (Figure 2) we observed a total of 8 clusters, via the examination of the protein-protein interaction network in Cytoscape using the MCODE plugin. MCODE scores for these clusters were as follows; cluster 1 = 36.571 cluster 2 = 6.643 cluster 3 = 4.4 cluster 4 = 4 cluster 5 = 3.5, cluster 6 = 3.3, cluster 7 = 3.2, cluster 8 = 2.6.

3.3 Grape Seed Components Go and Kegg Enrichment Analysis Against Psoriasis

The process of enriching Biological Process (BP), Molecular Function (MF), and Cellular Component (CC) for 232 frequent targets of grape seed and psoriasis were studied using the Shiny GO database. A dot bar chart (Figure 3) was made using the top 20 items selected using the FDR (-log 10) as a basis. The key biological processes identified by GO analysis are reaction to oxygen-containing compounds, control of cell population growth, and cellular response to oxygen-containing compounds, involved in the constituents related to grape seed. Cellular components saw significant enrichment in cell surface, secretory granule, membrane raft, membrane microdomain, etc. The MF was mainly enriched, in among the activities that have been found are signaling receptor binding, molecular transducer signalling receptor action. A combined graph of Gene ontology analysis based on fold enrichment (Figure 3).

The 232 common targets were used in KEGG pathway enrichment research. Top 20 paths in (Figure 4) are shown as a dot bar graph, selected using the -log 10 (FDR). The KEGG pathway investigation found that the route with the greatest degree of enrichment was linked to many pathways, including the HIF-1 signaling system, the AGE-RAGE regulating pathway, and pathways of cancer. Additionally, important psoriasis genes gravitated towards were those associated to Th17 cell differentiation and PI3K-Akt

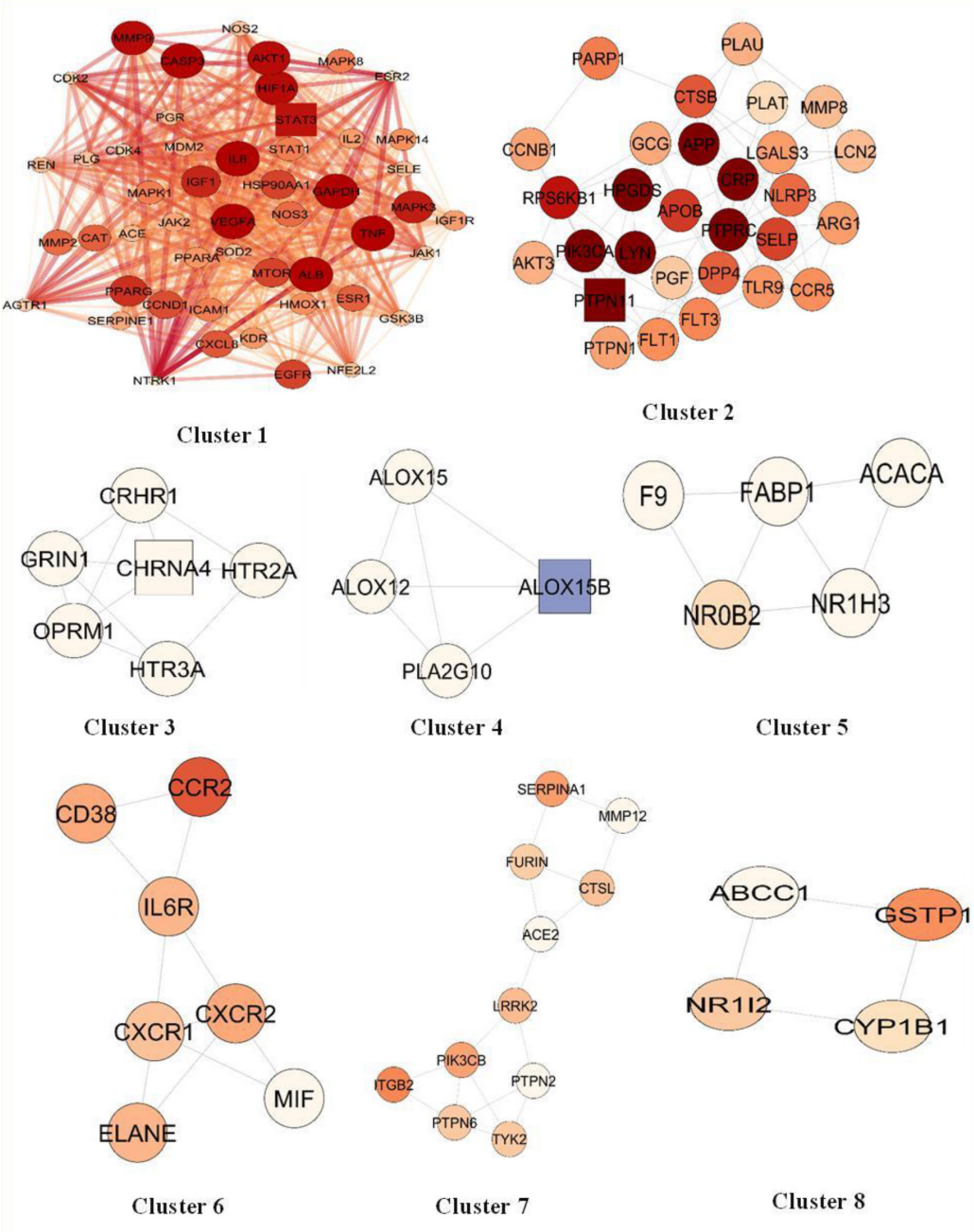


Figure 2. Clusters that obtained through MCODE analysis in Cytoscape software, all the hub proteins were identified in cluster 1, square shape of the protein in the cluster is the seed of the cluster where origin of the cluster happens and sphere shape of the proteins where these proteins clustered around the seed protein.

signaling pathways, cancer development (particularly pancreatic and prostate cancer), formation of new blood vessels (EGFR tyrosine kinase inhibitor resistance).

With the help of Cytoscape 3.6.0, we were able to construct the "Grape seed constituent-Target-Psoriasis-Pathway" network diagram according to the twenty signal pathways found using KEGG enrichment analysis. The degree (Figure 5) was used to adjust the size of the network nodes.

The network shows most of the genes were gravitated towards Pathways of cancer and PI3K-AKT Pathway (Table 3) and the target proteins were mostly connected to bioactives like Procyanidin B1, Procyanidin B3, Procyanidin B4 etc., (Table 4). A KEGG enrichment analysis of top 20 pathways (Table

Table 2. Top 20 Hub proteins obtained from Cytohubba extension MCC method of Cytoscape software

Rank	Protein	Name	Score
1	VEGFA	Vascular Endothelial Growth Factor A	2.02E+21
2	GAPDH	Glyceraldehyde-3-Phosphate Dehydrogenase	2.02E+21
3	CASP3	Cysteine-Aspartic Protease 3	2.02E+21
4	ALB	Albumin	2.02E+21
5	TNF	Tumor Necrosis Factor	2.02E+21
6	IL6	Interleukin 6	2.02E+21
7	MMP9	Matrix Metallopeptidase 9	2.02E+21
8	AKT1	AKT Serine/Threonine Kinase 1	2.02E+21
9	MAPK3	Mitogen-Activated Protein Kinase 3	2.00E+21
10	IGF1	Insulin-Like Growth Factor 1	1.99E+21
11	HIF1A	Hypoxia-Inducible Factor 1 Alpha	1.90E+21
12	STAT3	Signal Transducer and Activator of Transcription 3	1.90E+21
13	MTOR	Mechanistic Target of Rapamycin	1.85E+21
14	HSP90AA1	Heat Shock Protein 90 Alpha Family Class A Member 1	1.85E+21
15	MAPK8	Mitogen-Activated Protein Kinase 8	1.83E+21
16	CCND1	Cyclin D1	1.83E+21
17	EGFR	Epidermal Growth Factor Receptor	1.73E+21
18	MAPK14	Mitogen-Activated Protein Kinase 14	1.65E+21
19	MAPK1	Mitogen-Activated Protein Kinase 1	1.49E+21
20	STAT1	Signal Transducer and Activator of Transcription 1	1.37E+21

5). As indicated in (Table 6) the top 20 nodes were chosen as the major targets of grape seed contents based on the Degree. Throughout the PI3K-AKT signaling cascade, the distribution of essential hub cluster proteins is clearly seen. An overview of the PI3K-AKT pathway's distribution of core targets is shown in (Figure 6). A Sankey plot was also drawn that shows distribution of proteins among the pathways that represents gene ratio, the colour of the dots represents -log 10 (P value), red colour dots were the significant pathways. The number of genes involved in the pathway is correlated with the size of the dots, which shown that PI3K-AKT signaling is the key pathway with high gene count and low -log 10 (P value) shown in (Figure 7).

3.4 Drug Likeliness Adme Parameters Estimation of Grape Seed Bioactives

The bioactives of grape seed was screened for drug likeness in Schrödinger Qikprop module and the obtained values are shown in (Table 7).

3.5 Molecular Docking of Grape Seed Bioactives with Psoriasis Core Targets

As consequence of the PPI network and "Grape seed constituents-target-Psoriasis-Pathway" diagram of a network, AKT1, ALB, HSP90AA1, MAPK8, CDK2, EGFR, ESR1 and IGF1R were selected for the molecular docking investigation, assuming them as the main candidates. These proteins were selected from PDB database based on the criteria of homo sapiens and no mutations. The RMSD values of these core proteins calculated in Schrödinger software with values below 2 are shown in (Table 8), this represents the protein is good for performing docking studies. The docking score was in the form of negative value if it was -5 or below, it was considered good. A better grade docking activity is correlated with a lower binding energy value. The scores of docking and amino acids participated in hydrogen bond formation and other interactions are in (Tables 9-14) where the prominent interactions to observe is hydrogen bonds and the amino acids that formed these bonds which results in strong

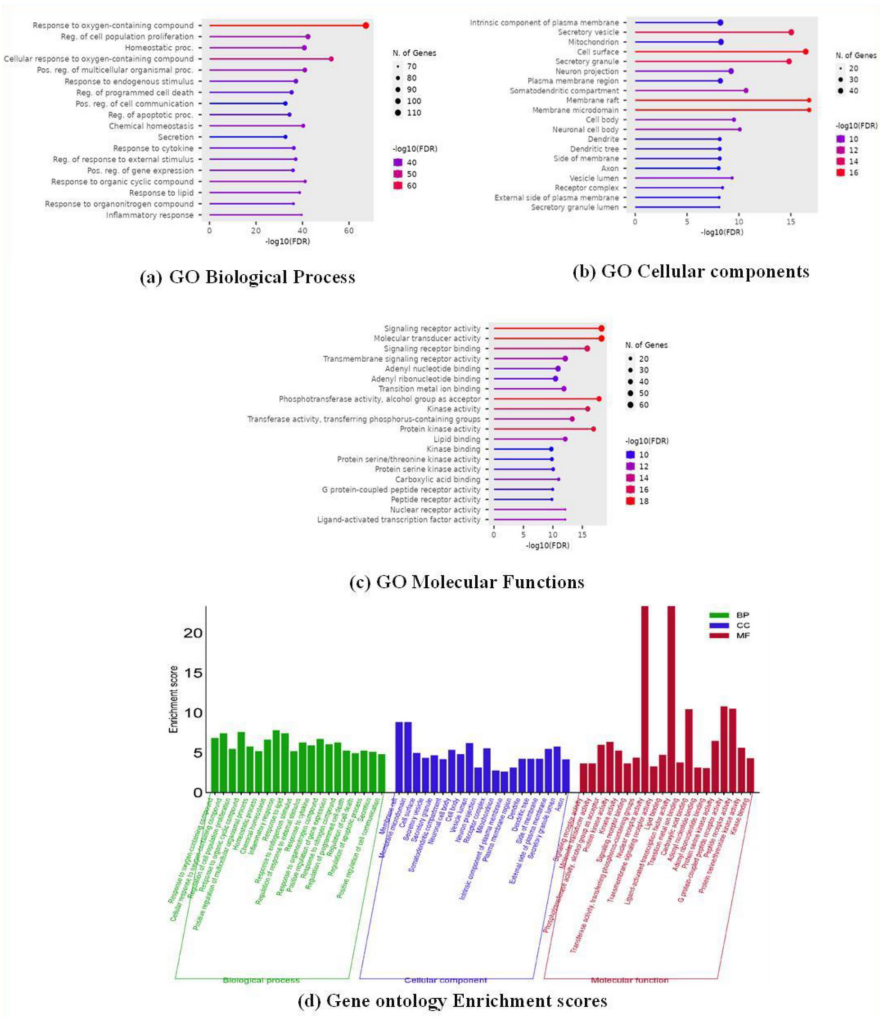


Figure 3. Gene Ontology studies of the common targets of grape seed constituents and psoriasis. **(a).** Biological process of the selected target proteins was shown red colour represents highest possibility in that particular activity. **(b).** The activity of the selected target proteins in cellular components. **(c).** Molecular functions that can be performed by the selected target proteins. **(d).** Enrichment scores of the above performed Gene ontology studies.

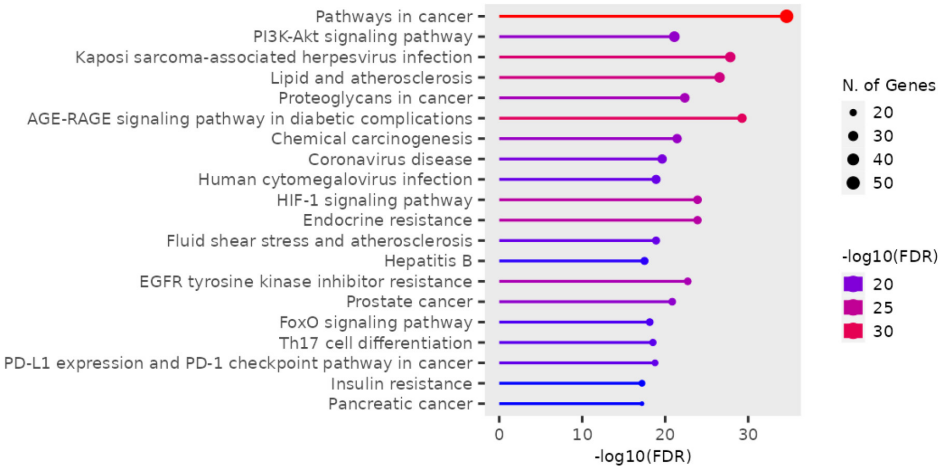


Figure 4. KEGG Pathway Enrichment analysis of the common targets of grape seed constituents and psoriasis.

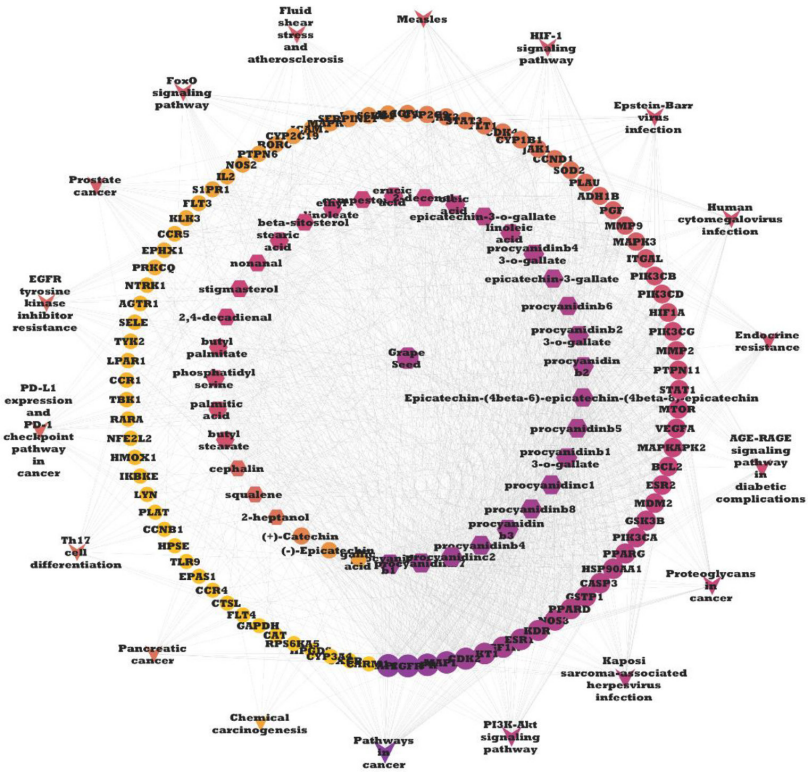


Figure 5. Network of Grape seed bioactive-Target-Pathway that constructed based on KEGG Enrichment analysis. Darker the colour of the node represents higher participation of the bioactives, targets, and pathways in the psoriasis disease and lighter the colour, lesser the participation.

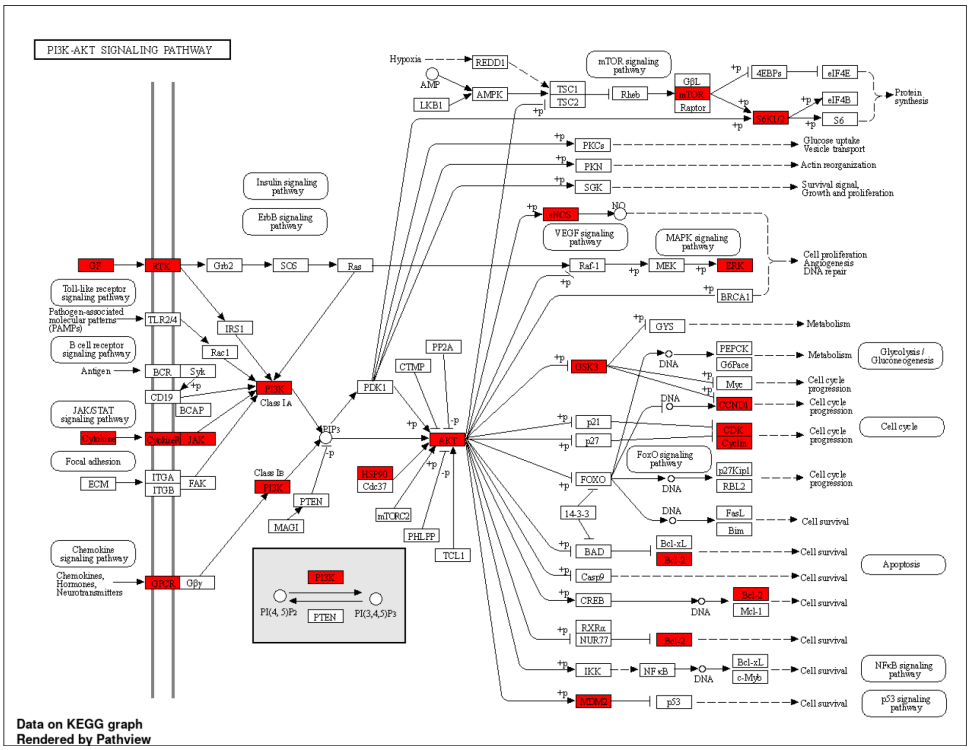


Figure 6. PI3K-AKT pathway, red colour boxes were the protein targets that belong to grape seed bioactives and psoriasis disease.

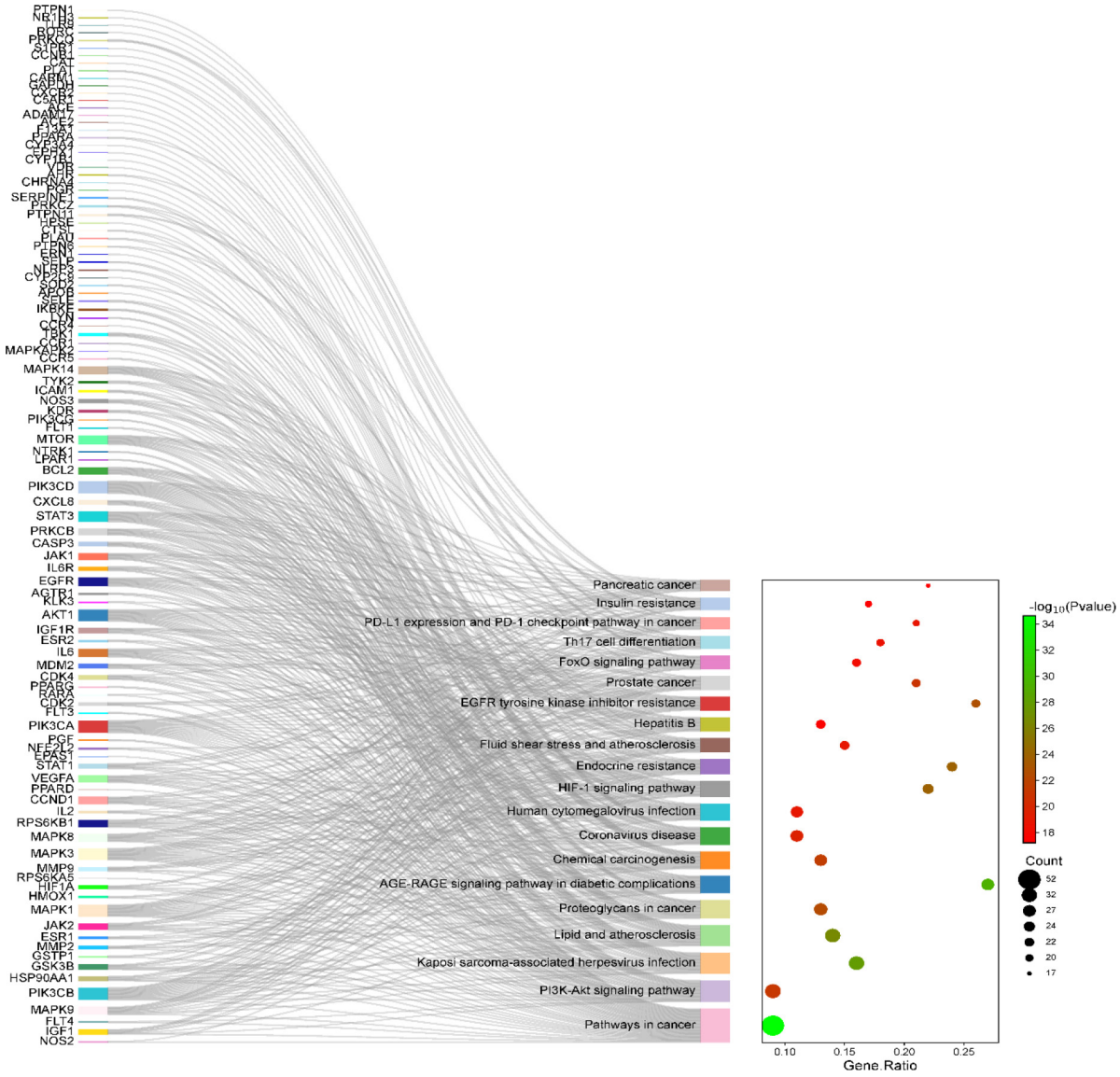


Figure 7. Sankey plot, that exhibited protein targets of different pathways, Gene counts and their -Log10 (P values).

interactions were observed, most of the proteins also showed other kind of interactions like Pi-cation, Pi-Pi Stacking etc., and amino acids that participated to form such interactions was also observed. The main criteria to observe is always Hydrogen bonds, later followed by Salt bridges, some components have these salt bridges, because they decide the binding strength that's how good dock scores around -9 to -10 can be obtained.

Grape seed bioactive exhibits strong affinity in terms of binding activity for AKT1, ALB, HSP90AA1, MAPK8, CDK2, ESR1, EGFR, and IGF1R. Among them HSP90AA1, AKT1, EGFR and IGF1R having the highest binding activity with Procyanidin B4, Procyanidin B6 and Procyanidin B7. These main bioactives of Grape seed can be inferred to lower oxidative stress and inhibit the production of inflammatory mediators by acting on the above-mentioned target proteins and can prevent the progression of psoriasis. Molecular docking details of good dock scores of bioactives with each protein are shown in (Figures 8-12).

3.6 Molecular Dynamics Simulation

We conducted dynamic simulations for three protein complexes; Procyanidin b4- EGFR, Procyanidin b6-AKT1 and Procyanidin b4-HSP90AA1, (Figure 13). All three of these proteins—AKT1, HSP90AA1,

Table 3. Pathways that obtained from KEGG Enrichment analysis arranged based on degree parameter obtained from Grape seed bioactive-target-pathway network

S. No.	Pathways	Degree
1	Pathways in cancer	49
2	PI3K-Akt signaling pathway	32
3	Kaposi sarcoma-associated herpesvirus infection	31
4	Proteoglycans in cancer	27
5	AGE-RAGE signaling pathway in diabetic complications	24
6	Endocrine resistance	23
7	Epstein-Barr virus infection	23
8	Human cytomegalovirus infection	23
9	HIF-1 signaling pathway	22
10	Fluid shear stress and atherosclerosis	21
11	FoxO signaling pathway	21
12	Measles	21
13	Prostate cancer	21
14	EGFR tyrosine kinase inhibitor resistance	19
15	PD-L1 expression and PD-1 checkpoint pathway in cancer	19
16	Th17 cell differentiation	18
17	Pancreatic cancer	17
18	Chemical carcinogenesis	8

and EGFR—maintained stable molecular structures throughout the simulation. Overall, the binding of Procyanidins, to proteins HSP90AA1, AKT1 stayed more consistent than EGFR, aligned with the predicted binding sites from docking. The interactions between these complexes were observed to be strong. The analysis of ligand protein RMSD confirmed the robustness of the binding interactions, between each protein and its respective ligand. (Figures 14-16) are visual representations obtained from specific molecular simulations.

4. Discussion

Psoriasis is a skin condition that causes long term inflammation and affects, around 1-3% of people in countries[25]. It has a substantial impact on the overall quality of life for individuals affected, resulting in feelings of humiliation and cognitive challenges[26,27]. Moreover psoriasis has been linked to health

Table 4. Bioactives that arranged based on degree parameter obtained from Grape seed bioactive-target-pathway network

S. No.	Grapeseed Bioactives	Degree
1	Procyanidin b1	42
2	Procyanidin b3	41
3	Procyanidinb4	41
4	Procyanidinb7	41
5	Procyanidinc2	41
6	Procyanidinb8	40
7	Procyanidinc1	40
8	Procyanidin b2	38
9	Procyanidinb5	38
10	Procyanidinb1 3-o-gallate	38
11	Epicatechin-(4beta-6)-epicatechin-(4beta-8)-epicatechin	38
12	Procyanidinb2 3-o-gallate	37
13	Epicatechin-3-gallate	36
14	Procyanidinb6	36
15	Procyanidinb4 3-o-gallate	35
16	Epicatechin-3-o-gallate	33
17	Linoleic acid	33
18	Oleic acid	31
19	2-decenal	28
20	Erucic acid	28
21	Campesterol	27
22	Ethyl linoleate	27
23	2,4-decadienal	26
24	Beta-sitosterol	26
25	Nonanal	26
26	Stigmasterol	26
27	Stearic acid	26
28	Phosphatidyl serine	24
29	Butyl palmitate	24
30	Palmitic acid	23
31	Butyl stearate	23
32	Cephalin	19
33	Squalene	19
34	2-heptanol	17
35	(+)-catechin	14
36	(-)-epicatechin	11
37	Gallic acid	9

Table 5. KEGG Pathway Enrichment analysis, distribution psoriasis related genes among the pathways

Pathways	No. of Genes of interest	Enrichment FDR
Pathways in cancer	52	2.32E-35
AGE-RAGE signaling pathway in diabetic complications	27	5.49E-30
Kaposi sarcoma-associated herpesvirus infection	32	1.44E-28
Lipid and atherosclerosis	32	2.77E-27
Endocrine resistance	23	1.27E-24
HIF-1 signaling pathway	24	1.27E-24
EGFR tyrosine kinase inhibitor resistance	21	1.92E-23
Proteoglycans in cancer	28	4.32E-23
Chemical carcinogenesis	27	3.70E-22
PI3K-Akt signaling pathway	33	7.86E-22

Table 5. Continued...

Pathways	No. of Genes of interest	Enrichment FDR
Prostate cancer	21	1.42E-21
Coronavirus disease	27	2.32E-20
Human cytomegalovirus infection	26	1.26E-19
Fluid shear stress and atherosclerosis	22	1.26E-19
PD-L1 expression and PD-1 checkpoint pathway in cancer	19	1.68E-19
Th17 cell differentiation	20	3.03E-19
FoxO signaling pathway	21	7.26E-19
Hepatitis B	22	3.11E-18
Insulin resistance	19	6.26E-18
Pancreatic cancer	17	6.26E-18

Table 6. Top 20 proteins that obtained from Grape seed bioactive-target-pathway network based on degree as topological parameter

Protein	Name	Betweenness centrality	Closeness centrality	Degree
EGFR	Epidermal growth factor receptor	0.033607074	0.578313253	47
MAPK1	Mitogen-activated protein kinase 1	0.036673744	0.578313253	47
MAPK14	Mitogen-activated protein kinase 14	0.030815882	0.564705882	45
MAPK8	Mitogen-activated protein kinase 8	0.029830448	0.560311284	44
CDK2	Cyclin-dependent kinase 2	0.025817805	0.555984556	42
AKT1	AKT serine/threonine kinase 1	0.026020281	0.543396226	40
ESR1	Estrogen receptor 1	0.018948331	0.539325843	39
IGF1R	Insulin-like growth factor 1 receptor	0.020157341	0.535315985	39
KDR	Kinase insert domain receptor	0.015305455	0.519855596	36
NOS3	Nitric oxide synthase 3	0.015402888	0.516129032	35
PPARD	Peroxisome proliferator-activated receptor delta	0.012543584	0.516129032	34
HSP90AA1	Heat shock protein 90 alpha family class A member 1	0.0133473	0.505263158	33
CASP3	Caspase 3	0.015379177	0.516129032	33
GSTP1	Glutathione S-transferase pi 1	0.018840007	0.516129032	33
PPARG	Peroxisome proliferator-activated receptor gamma	0.011166172	0.508833922	32
GSK3B	Glycogen synthase kinase 3 beta	0.012185746	0.494845361	30
PIK3CA	Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha	0.01430995	0.491467577	30
ESR2	Estrogen receptor 2	0.00867562	0.488135593	28
MDM2	MDM2 proto-oncogene	0.011160401	0.494845361	28
MAPKAPK2	Mitogen-activated protein kinase-activated protein kinase 2	0.008446916	0.488135593	27

Table 7. Grape seed constituents drug likeliness parameters estimation in Qikprop module of Schrodinger software

S. No.	Compound	mol_MW	QPlogBB	accptHB	QPlogKp	Human Oral Absorption	Rule of Three	Rule of Five
	Range for recommended values	130.0–725.0	–3.0 – 1.2	2.0 – 20.0	–8.0 – –1.0	1 - low, 2- medium, 3- high	maximum is 3	maximum is 4
1	(+)-Catechin	290.272	-1.91	5.45	-4.731	2	1	0
2	(-)-Epicatechin	290.272	-1.815	5.45	-4.662	2	1	0
3	2,4-Decadienal	152.236	-0.63	2	-2.269	3	0	0
4	2-Decenal	154.252	-0.634	2	-2.34	3	0	0
5	2-Heptanol	116.203	-0.082	1.7	-1.802	3	0	0
6	Beta-sitosterol	414.713	-0.327	1.7	-1.635	1	1	1
7	Campesterol	400.687	-0.268	1.7	-1.731	1	1	1
8	Cephalin	299.217	-1.982	10	-6.867	2	1	0
9	Epicatechin-3-gallate	442.378	-3.655	8	-6.759	2	2	1
10	Epicatechin-3-o-gallate	442.378	3.655	8	-6.759	2	2	1
11	Gallic acid	170.121	-1.659	4.25	-5.488	2	1	0
12	Linoleic acid	280.45	-1.265	2	-1.953	3	0	1
13	Nonanal	142.241	-0.51	2	-2.195	3	0	0
14	Oleic acid	282.465	-1.374	2	-2.02	3	0	1
15	Palmitic acid	256.428	-1.492	2	-2.185	3	0	1
16	Procyanidin b1	578.528	-4.614	10.9	-7.174	2	2	2
17	Procyanidin b2	578.528	-4.48	10.9	-7.026	2	2	2
18	Procyanidin b3	578.528	-3.801	10.9	-7.044	2	2	2
19	Procyanidinb4	578.528	-3.684	10.9	-6.854	2	2	2
20	Procyanidinb5	578.528	-4.548	10.9	-6.892	2	2	2
21	Procyanidinb6	578.528	-4.539	10.9	-6.832	2	2	2
22	Procyanidinb7	578.528	-4.66	10.9	-6.964	2	2	2
23	Procyanidinb8	578.528	-4.421	10.9	-6.76	2	2	2
24	Squalene	410.725	1.566	0	-1.058	1	2	1
25	Stigmasterol	412.698	-0.27	1.7	-1.731	1	1	1
26	Butyl stearate	340.588	-1.306	2	-0.726	2	1	1
27	Stearic acid	284.481	-1.506	2	-1.777	2	1	1
28	Procyanidinc2	720.784	-5.612	16.35	-8.326	2	2	2
29	Procyanidinc1	720.784	-7.273	16.35	-8.475	2	2	2
30	Procyanidinb1 3-o-gallate	723.634	-4.416	13.45	-7.97	2	2	2
31	Procyanidinb2 3-o-gallate	724.634	-5.861	13.45	-8.971	2	2	2
32	Procyanidinb4 3-o-gallate	724.634	-6.518	13.45	-8.682	2	2	2
33	Phosphatidyl serine	722.084	-3.565	12	-2.101	2	3	2
34	Butyl palmitate	312.535	-1.155	2	-0.917	1	1	1
35	Ethyl linoleate	308.503	-0.967	2	-0.985	1	1	1
36	Erucic acid	338.573	-1.812	2	-1.465	2	1	1
Epicatechin-(4beta-6)-epicatechin-(4beta-8)-epicatechin								

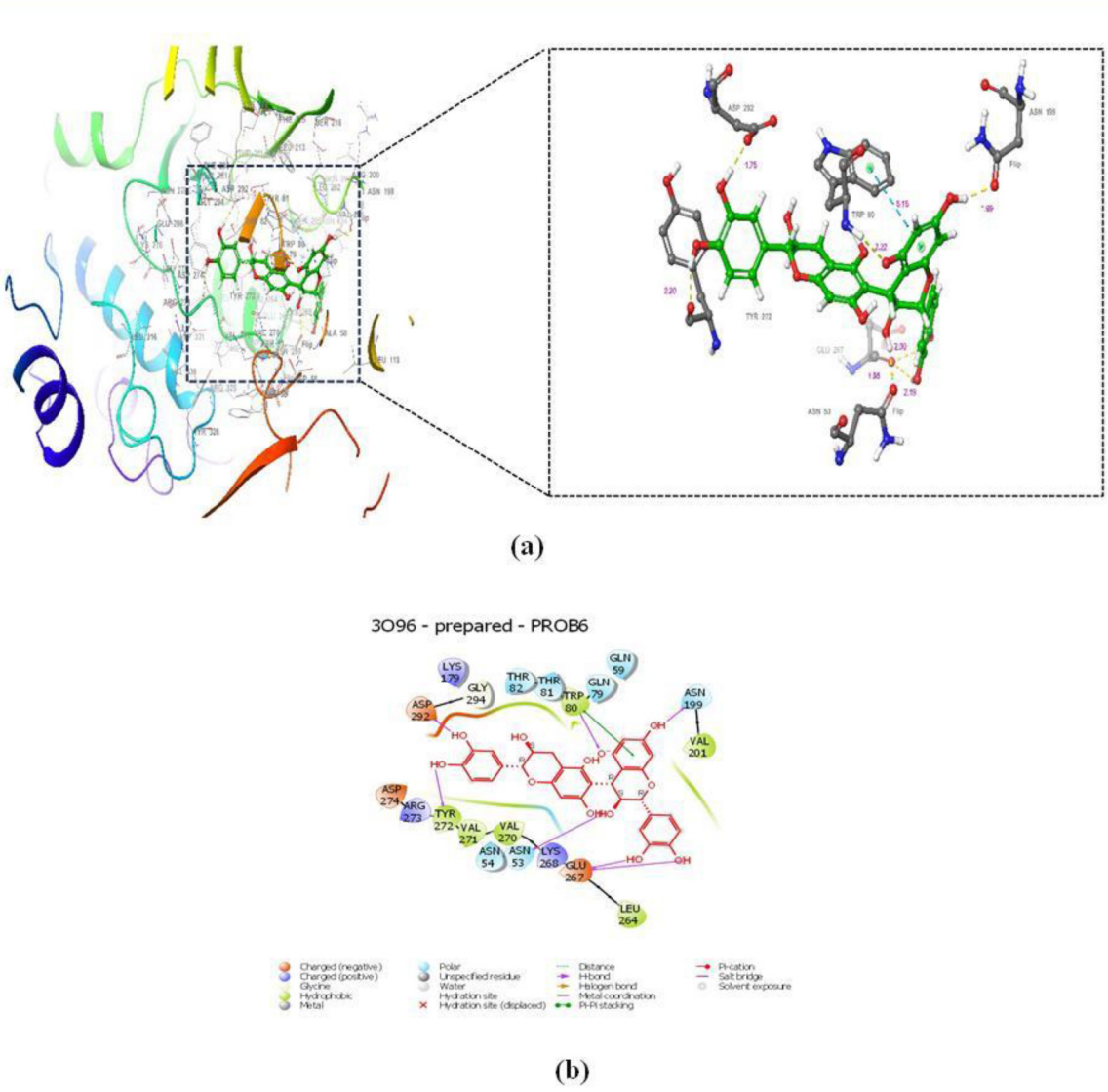


Figure 8. Molecular docking analysis of AKT1 and Procyanidin B6. **(a).** 3D structure of Procyanidin B6 with bond lengths and amino acids of the AKT1 protein interacted with the ligand. **(b).** 2D structure of the AKT1-Procyanidin B6 interaction.

issues like metabolic syndrome and cardiovascular diseases[28,29]. Due to its prevalence and impact extensive research has been conducted to understand the disease including treatment goals, disease occurrence and potential therapeutic targets[30,31]. Additionally there is a growing interest in studying the connection among psoriasis and alcoholic fatty liver disease highlighting the importance of comprehensively understanding this condition and its broader implications on the body[32,33]. Over time managing psoriasis has evolved to prioritize reaching treatment targets through the use of therapies[34,35]. These advancements have greatly improved care by addressing issues. It emphasizes the significance of setting treatment goals as part of management for individuals, with psoriasis[36].

Herbal therapies work through complex systems with many bioactives and targets. Analysis of the effectiveness of an herbal therapy is made more difficult when there is uncertainty about the pathophysiology of the disease. Systematic network analysis and pharmacology are combined in network pharmacology. It permits a systematic analysis of the bioactives, targets, and pathways of medication at the molecular level,

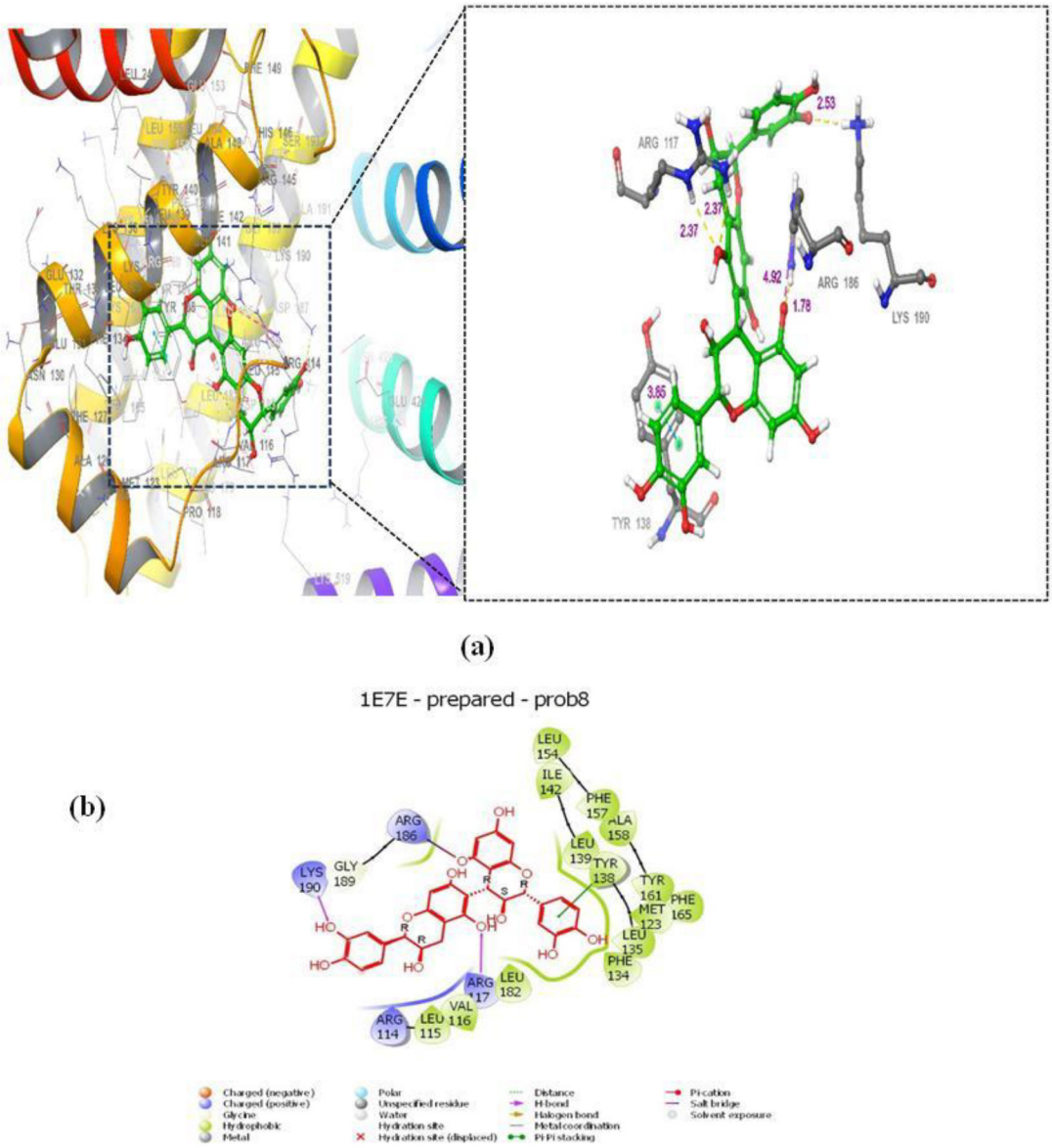


Figure 9. Molecular docking analysis of Albumin and Procyanidin B8. **(a).** 3D structure of Procyanidin B8 with bond lengths and amino acids of the albumin protein interacted with the ligand. **(b).** 2D structure of the Albumin-Procyanidin B8 interaction.

improving our understanding of how these interact. Network pharmacology, molecular docking, and dynamic simulations provide valuable insights, their reliability and potential biases merit consideration for accurate interpretation of results.

Common proteins that were obtained from Venn intersection diagram were the essential proteins related to psoriasis and grape seed constituents. The obtained 232 proteins were numerous to find the potential proteins related to psoriasis, regarding the grape seed constituents. Analytical techniques like STRING PPI network analysis, Cytohubba application of Cytoscape for hub protein identification and KEGG enrichment analysis were used to identify the key pathways. AKT1, ALB, EGFR, HSP90AA1, IGF1R, TNF, IL6 etc., were the essential proteins that play key role in psoriasis, the grape seed constituents act on regulating these proteins that can reduce the psoriasis. PI3K-AKT pathway, Th17 cell differentiation, FOXO Signaling pathway were key pathways that the above-mentioned potential proteins were involved. These pathways perform a significant part in pathophysiology of psoriasis. Multifaceted

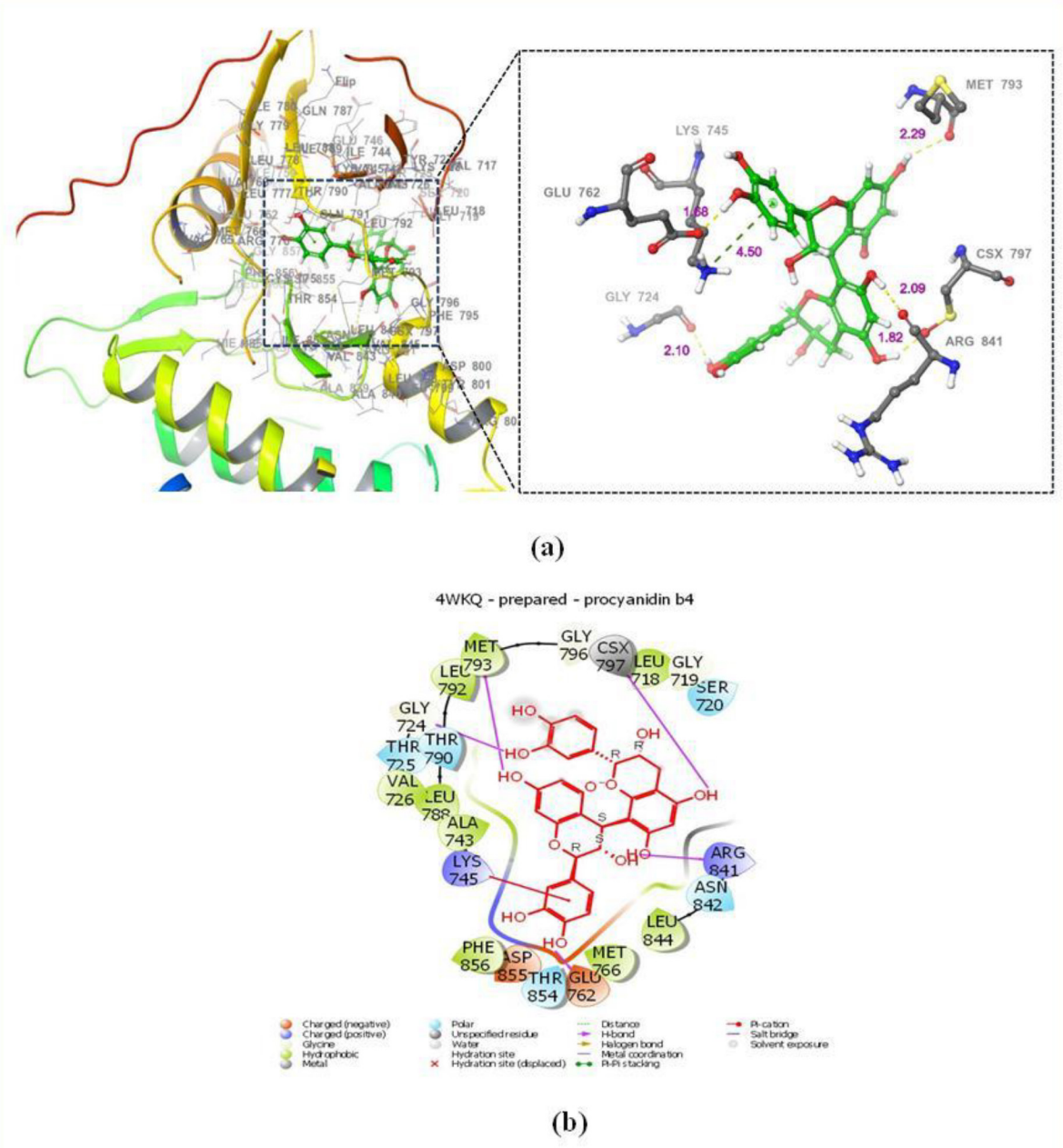


Figure 10. Molecular docking analysis of EGFR and Procyanidin B4. **(a).** 3D structure of Procyanidin B4 with bond lengths and amino acids of the EGFR protein interacted with the ligand. **(b).** 2D structure of the EGFR-Procyanidin B4 interaction.

pathways were regulating psoriasis, it has complexity to identify which pathway has crucial role in regulating this disease, but network pharmacology has become very helpful in identifying the key pathways related to the psoriasis through potential protein targets that were identified through network analysis.

Grape seed constituents like Procyanidin B1, B3, B4, B7 and other bioactives (Table 4) regulate these identified potential proteins therefore affecting the pathways responsible for pathophysiology of psoriasis. These compounds have been found to possess properties such, as anti-inflammatory and immune modulating effects[37-39]. The primary reason for the high antioxidant capacity of grape seeds is the presence of trimeric, oligomeric, or polymeric procyanidins, which greatly enhance their antioxidant properties[40,41]. These findings propose that grape seed constituents could serve as a tool for managing psoriasis and

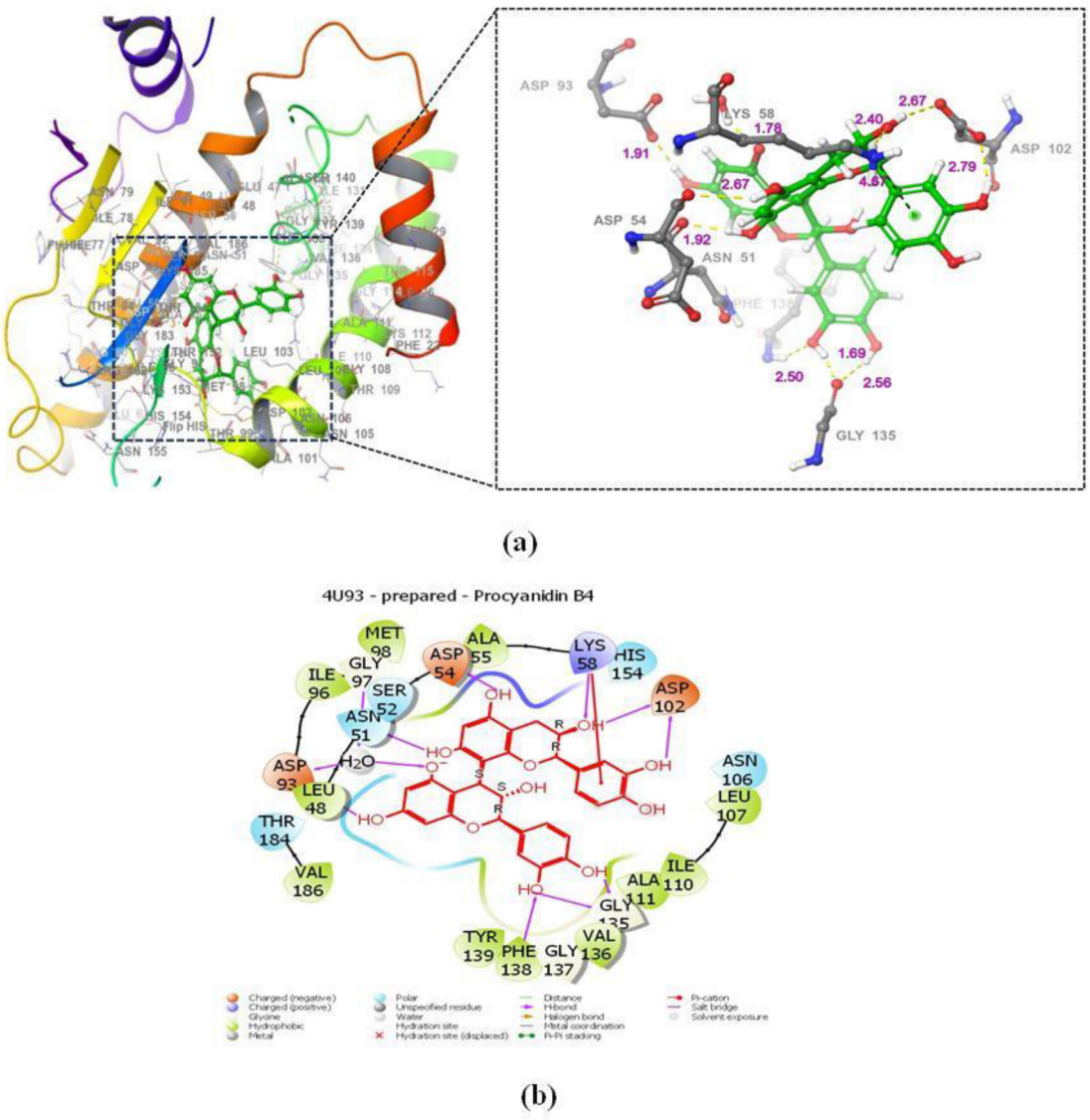


Figure 11. Molecular docking analysis of HSP90AA1 and Procyanidin B4. **(a).** 3D structure of Procyanidin B4 with bond lengths and amino acids of the HSP90AA1 protein interacted with the ligand. **(b).** 2D structure of the HSP90AA1-Procyanidin B4 interaction.

possibly contribute to the development of therapeutic approaches, for this condition. To further validate these proteins were subjected to molecular docking studies.

Among the many health benefits provided by the bioactive chemicals found in grape seeds are their actions as antioxidant, anti-inflammatory, anticancer, and antibacterial. These findings propose that grape seed constituents could serve as a tool for managing psoriasis and possibly contribute to the development of therapeutic approaches, for this condition. In the network of PPI 232 targets of Grape seed constituents acting in Psoriasis, TNF, AKT1, ALB, IL6, GAPDH, VEGFA, EGFR, MAPK3, STAT3, etc., were among the top twenty protein targets based on node degree (Table 1). These proteins are classified as core proteins and likely have significant contribution in the therapeutic impact of Grape seed on Psoriasis. These proteins were also analysed for hub proteins through Cytohubba plugin in Cytoscape which gave top 20 proteins, based on MCC algorithm, which were VEGFA, GAPDH, CASP3, ALB, TNF, IL6 etc., (Table 2). Further PPI network was also observed for clusters through MCODE analysis in Cytoscape total 8

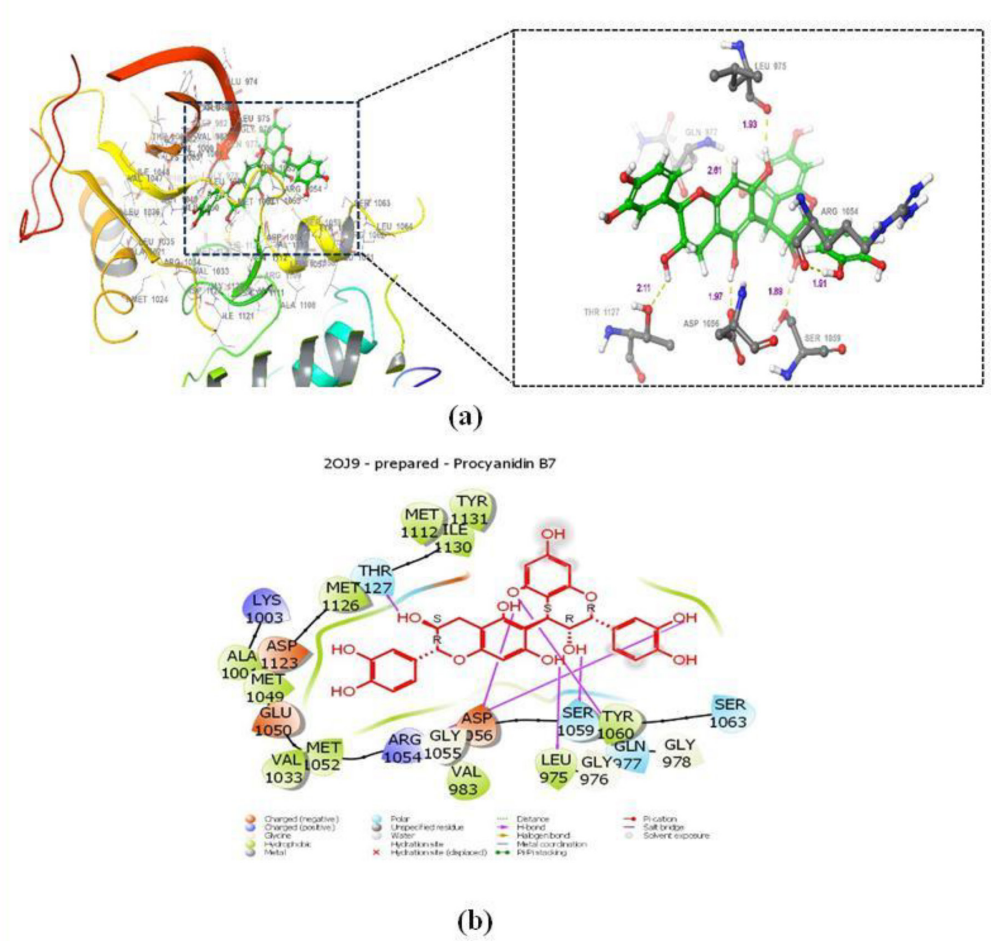


Figure 12. Molecular docking analysis of IGF1R and Procyanidin B7. (a). 3D structure of Procyanidin B7 with bond lengths and amino acids of the IGF1R protein interacted with the ligand. (b). 2D structure of the IGF1R-Procyanidin B7 interaction.

Table 8. Proteins selected for molecular docking studies based on RMSD values

S. No.	PROTEIN	PROTEIN NAME	RMSD
1	AKT1 (3O96)	RAC-alpha serine/ threonine-protein kinase	1.7800
2	ALB (1E7E)	Albumin	1.7800
3	EGFR (4WKQ)	Epidermal growth factor receptor	0.9123
4	HSP90AA1 (4U93)	Heat shock protein HSP 90-alpha	2.7447
5	MAPK8 (3ELJ)	Mitogen-activated protein kinase 8	1.0115
6	CDK2 (3PY0)	Cyclin-dependent kinase 2	0.2938
7	ESR1 (3ERT)	Estrogen receptor	1.6244
8	IGF1R (2OJ9)	Insulin-like growth factor 1 receptor	0.5471

clusters were observed in the network in which the first cluster has all the potential proteins that observed in node degree and MCC algorithm, thus potential targets for psoriasis related to grape seed were identified.

The proteins identified in grape seed for psoriasis can be categorized into several groups based on their roles in the pathophysiology of psoriasis. TNF-α, AKT1, ALB, IL6, VEGFA, EGFR, MAPK3, and STAT3 are implicated in the inflammatory and immune dysregulation processes associated with psoriasis[42,43]. TNF-α, in particular, plays a critical role in the pathogenesis of psoriasis, as it is strongly associated with IL-23 and Th17 effector cytokines, which are key drivers of the autoimmune linked chronic inflammatory skin disease[44,45]. Additionally, TNF-α has been related to the development and maintenance of psoriatic lesions[46]. Furthermore, AKT1, EGFR, and MAPK3 are

Table 9. Molecular docking scores and the bond interactions of protein AKT1 and ligands

Protein	Ligand	Docking score	Hydrogen bonds	Other interactions
AKT1 (3O96)	Epicatechin-3-o-gallate	-9.754	ASN53, GLN79, TRP80, THR211, ILE290	-
	Oleic Acid	-9.543	GLN79, GLU85, TYR272, ASP274	Pi-cation- ARG273
	Quercitin-3′-glucoside	-9.367	GLN79, THR82, TYR272, ARG273, ASP274	Pi-Pi Stacking- TRP80
	Procyanidin b6	-9.272	ASN53, TRP80, ASN199, TYR272, GLU267, ASP292	Pi-Pi Stacking- TRP80
	Epicatechin-3-gallate	-9.007	GLN79, THR82, SER205, TYR272	Pi-Pi Stacking- TRP80
	Quercitin-3′-glucoside	-8.981	ASN53, GLN79, TRP80, LYS268	Pi-Pi Stacking- TRP80
	Quercitin-3′-glucoside	-8.796	GLN79, THR82, ASP274	Pi-Pi Stacking- TRP80
	Quercetin	-8.615	GLN79, SER205, THR211	Pi-Pi Stacking- TRP80
	Epicatechin-3-o-gallate	-8.592	ASN53, GLN79, TRP80, THR211, ILE290	Salt bridge- LYS268
	(-) Epicatechin	-8.324	GLN79, SER205	Pi-Pi Stacking- TRP80
	Quercitin-3′-glucoside	-8.298	GLU85, ASN54, TYR326, TYR272, VAL271, GLN79, ASP292	Pi-cation- ARG273
	Quercitin-3′-glucoside	-8.198	GLN79, GLU85, TYR272, ASP292, GLY294	Pi-cation- ARG273
	Quercitin-3′-glucoside	-8.06	GLN79, LYS268, TYR272, ASP292	Pi-Pi Stacking- TRP80
	Procyanidin b6	-8.049	ASN53, TRP80, ASN199, GLU267, TYR272, ASP292	Pi-Pi Stacking- TRP80
	Epicatechin-3-gallate	-7.974	GLN79, THR82, SER205, TYR272	Pi-Pi Stacking- TRP80, Salt bridge- LYS268
	Quercitin-3′-glucoside	-7.97	ASN53, GLN79, ASP292,	Pi-Pi Stacking- TRP80
	(+) Catechin	-7.913	TYR272, ASP292	Pi-Pi Stacking- TRP80
	Quercitin-3′-glucoside	-7.876	ASN54, GLN79, GLU85, TYR272, TYR326	Pi-cation- ARG273
	Procyanidin b7	-7.857	SER205, GLU267, VAL271, TYR272	-
	Myricetin	-7.751	ASN54, GLU85, ASP292, GLY294,	Pi-cation- ARG273
	Oleic acid	-7.635	ASN53, LYS268, ASN199, ILE290, THR211	-
	GSK690693-Std	-7.626	TRP80, ASP274	Salt bridge- ASP273, Pi-cation- TYR272 Pi-Pi Stacking- TRP80,

Table 10. Molecular docking scores and the bond interactions of protein ALB and ligands

Protein	Ligand	Docking score	Hydrogen bonds	Other interactions
ALB (1E7E)	Erucic acid	-8.583	LYS190	Salt bridge- ARG114, LYS190
	Taxifolin	-8.038	ARG117, LEU135	Pi-Pi Stacking- TYR161
	Procyanidin b8	-7.899	ARG117, LYS190	Salt bridge- ARG186, Pi-Pi stacking- TYR138
	Ruxolitinib-Std (Agonist)	-7.808	ARG117, ARG186	-

involved in pathways related to signaling that regulate cell proliferation, differentiation, and survival, which are dysregulated in psoriasis[47,48]. VEGFA is associated with angiogenesis, a process that is dysregulated in psoriatic skin. ALB has been implicated in wound healing, processes that are dysregulated in psoriatic skin. IL6 is involved in modulating tissue remodelling, angiogenesis, and promoting tumor cell survival, which are relevant to the pathogenesis of psoriasis[49]. The proteins found in grape seeds that are associated with psoriasis have roles in multiple biological processes including inflammation, immunological dysregulation, cell signaling, angiogenesis, tissue remodelling, and wound healing.

Table 11. Molecular docking scores and the bond interactions of protein EGFR and ligands

Protein	Ligand	Docking score	Hydrogen bonds	Other interactions
EGFR (4WKQ)	Kaempferol-3-o-glucoside	-9.918	GLU762, MET793, CSX797, ASN842, ASP855	-
	Quercetin-3'-glucoside	-9.716	LYS745, MET793, ARG841, ASN842, ASP855	-
	Quercetin-3'-glucoside	-9.695	MET793, ARG841, ASP855	-
	Quercetin-3'-glucoside	-9.562	LYS745, GLU762, MET793, CSX797, ASN842, ASP855	-
	Quercetin-3'-glucoside	-9.514	GLU762, MET793, CSX797, ASN842, ASP855	-
	Quercetin-3'-glucoside	-9.364	MET793, CSX797, ARG841, ASN842, ASP855	-
	Quercetin-3'-glucoside	-9.204	MET793, ASN842, ASP855	-
	Quercetin-3'-glucoside	-9.092	LEU718, GLU762, MET793, CSX797,	-
	Quercetin	-8.593	GLU762, MET793	-
	Procyanidin b4	-8.578	GLY724, LYS745, GLU762, MET793, CSX797, ARG841,	Pi-cation- LYS745
	Myricetin	-8.444	GLU762, MET793	-
	(+) Catechin	-7.91	GLU762, LEU788	-
	Taxifolin	-7.871	GLU762, LEU788, MET793	-
	Carnertinib-Std	-7.798	CSX797, MET793	Halogen bond- LYS745

Table 12. Molecular docking scores and the bond interactions of protein HSP90AA1 and ligands

Protein	Ligand	Docking score	Hydrogen bonds	Other interactions
HSP90AA1 (4U93)	Epicatechin-3-gallate	-10.936	ASP93, LEU103, GLY135, TRP162	-
	Procyanidin b4	-9.923	LEU48, ASN51, ASP54, LYS58, ASP102, GLY135, PHE138	Pi-cation- LYS58
	Epicatechin-3-gallate	-9.877	ASN51, ASP93, LEU103, GLY135, TRP162	-
	Procyanidin c1	-9.646	ASN51, ASP54, LEU107, GLN133, TYR139	-
	Procyanidin b8	-9.457	ASN51, ASP54, LYS58	Pi-Pi stacking- PHE138
	Epicatechin-3-o-gallate	-8.988	ASP54, ASP93, GLY135, PHE138	-
	BIIB021-Std	-8.982	ASP93, GLY97	Pi-Pi stacking- PHE138

We conducted a GO enrichment analysis on the 232 putative targets in order to ascertain the underlying mechanism responsible for the therapeutic advantages of Grape seeds in treating Psoriasis. The top 20 biological processes (Figure 3a) primarily associated with cytokines, apoptosis, reactive oxygen species, and the regulation of inflammation. Psoriasis progressions are linked to oxidative stress, prolonged inflammatory infiltration[50], inflammatory cell death[51], and oxidative stress[52]. This shows that multiple BPs depend on the main protein targets. The main targets that MFs were enriched in were signal receptor activity, molecular transducer activity, signaling receptor binding, and transmembrane signalling receptor activity (Figure 3b). Further demonstrates (Figure 3c) that CCs that were high in targets mostly consisted of secretory vesicle, cell surface, secretory granule, membrane raft, and membrane microdomain. These enriched functions involved potential targets that observed in PPI interactions. The pathological mechanism of psoriasis is complicated, as these results show.

Table 13. Molecular docking scores and the bond interactions of protein IGF1R and ligands

Protein	Ligand	Docking score	Hydrogen bonds	Other interactions
IGF1R (2OJ9)	Quercetin-3'-glucoside	-8.731	GLU1050, MET1052, ASP1056	-
	Kaempferol-3-o-glucoside	-8.637	THR1053, ASP1056, MET1126, THR1127	-
	Quercetin-3'-glucoside	-8.481	GLN977, GLU1050, MET1052, ASP1056	-
	Quercetin-3'-glucoside	-8.266	GLU1050, MET1052, ASP1056	-
	Quercetin-3'-glucoside	-8.078	GLU1050, MET1052, ASP1056, SER1059	-
	Quercetin-3'-glucoside	-8.027	GLN977, GLU1050, MET1052, SER1059	-
	Epicatechin-3-o-gallate	-8.013	LYS1003, MET1052, ASP1056, ASP1123	-
	Quercetin-3'-glucoside	-7.952	GLN977, GLU1050, MET1052, ASP1056	-
	Procyanidin b7	-7.792	THR127, LEU975, ARG1054, ASP1056, SER1059, TYR1060	-
	Epicatechin-3-o-gallate	-7.689	LYS1003, MET1052, ASP1123	-
	Quercetin	-7.591	GLU1050, MET1052, ASP1056	-
	Nvp-aew 541-Std	-7.587	GLU974	-

Table 14. Molecular docking scores and the bond interactions of proteins MAPK8, CDK2, ESR1 and ligands

Protein	Ligand	Docking score	Hydrogen bonds	Other interactions
MAPK8 (3ELJ)	Epicatechin-3-o-gallate	-8.966	GLU109, MET111, ASN156	-
	(-) Epicatechin	-8.69	MET111, ASN114, SER155, ASN156,	-
	(+) Catechin	-8.592	ILE32, MET111, ASN114, ASN156	-
	Epicatechin-3-o-gallate	-8.018	GLU109, MET111, ASN156	-
	Taxifolin	-7.921	GLN37, GLY38, ASN114, SER155	-
	Procyanidin b8	-7.757	SER34, MET111, SER155, TYR191	-
	Epicatechin-3-o-gallate	-7.653	MET111, ASN156	-
	JNK inhibitor VII-Std	-7.639	ARG69, ASN114, ASN156	-
CDK2 (3PY0)	(-) Epicatechin	-8.739	GLU12, LEU83, GLN131, ASN132	-
	Quercetin	-7.911	LEU83, ASP86, ASN132	-
	(+) Catechin	-7.805	GLU12, LEU83, ASN132	-
	Taxifolin	-7.746	GLU12, LEU83	-
	SU9516-Std	-7.745	GLU81, LEU83	Pi-Pi stacking- PHE80
ESR1 (3ERT)	(+) Catechin	-8.791	THR347, ASP351, GLU353	-
	Myricetin	-8.348	THR347, ASP351, GLU353, ARG394	-
	Taxifolin	-8.181	THR347, GLU353, ARG394	-
	Quercetin	-8.001	GLU353, ARG394	-
	Procyanidin b7	-7.651	THR347	-
	Propyl pyrazole triol-Std (Agonist)	-7.648	MET528, CYS530	-

We carried out a KEGG study of the 232 potential targets of grape seed acting in psoriasis to learn more about the potential mechanism of grape seed in treating psoriasis. In (Figure 4) you can see the pathways that are connected to psoriasis. These include the pathways in cancer, the PI3K-AKT signaling pathway, the AGE-RAGE signaling pathway, the development of Th17 cells, and more.

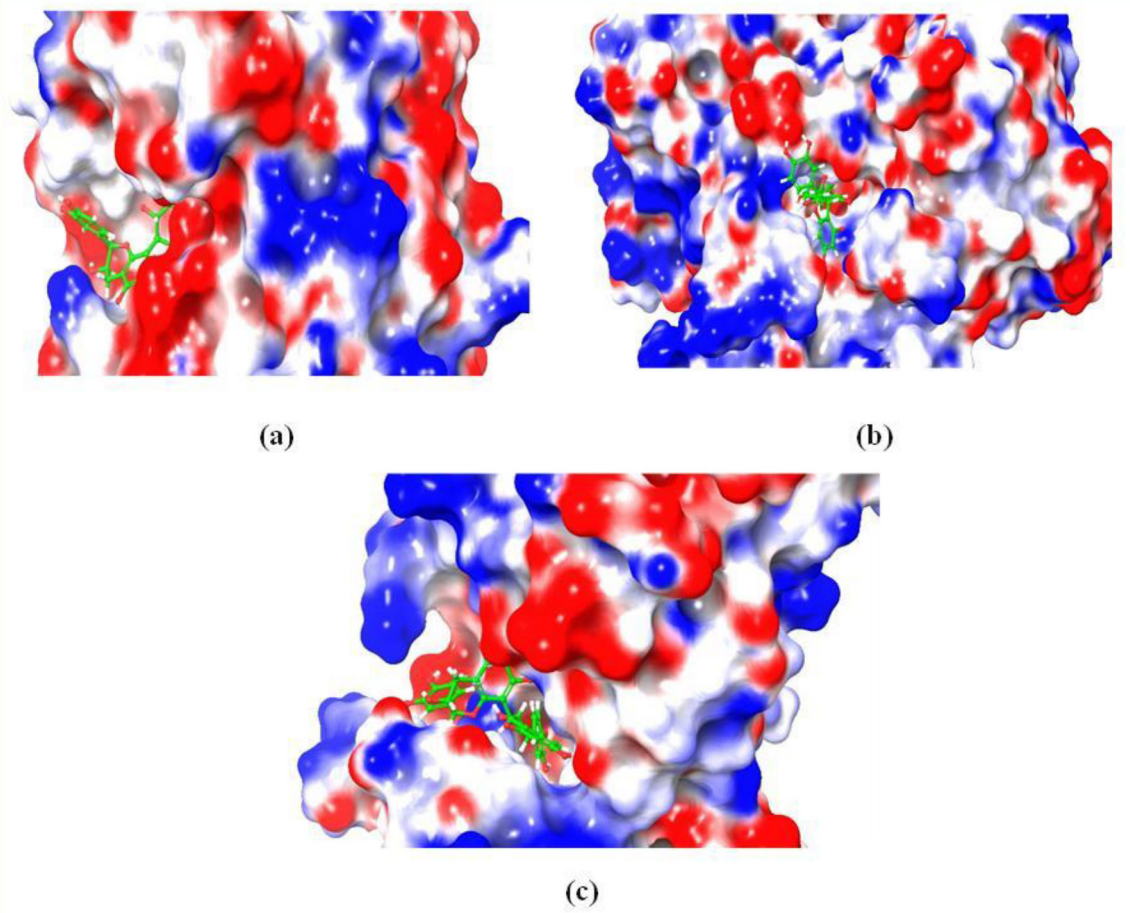


Figure 13. Molecular surface visualization of the selected protein-ligand complexes for MD-Simulation. **(a).** HSP90AA1-Procyanidin B4; **(b).** AKT1-Procyanidin B6; **(c).** EGFR-Procyanidin B4.

A network of Grape seed bioactives-targets-pathways (Figure 5) was constructed based on the KEGG enrichment and top 20 proteins was observed based on node degree such as EGFR, MAPK1, MAPK14, MAPK8, CDK2, AKT1 etc, (Table 6). Based on the Sankey plot of KEGG enrichment (Figure 7) and degree values in pathway network (Table 3) the potential genes of grape seed and psoriasis were concentrated in PI3K-AKT pathway (Figure 6). The use of grape seed bioactives to improve Psoriasis is likely linked to the PI3K-AKTsignal pathway and Th17 cell differentiation. Psoriasis can lead to the development of red, scaly areas on the skin due to increased cellular proliferation, initiation of cytokine release, and stimulation of Th17 cell proliferation.

The PI3K Akt signaling pathway has recently been shown to have a role in the control of cell death, autophagy, and proliferation, according to scientists, these activities are relevant to the development of psoriasis[53]. The initiation of psoriasis has been correlated with the PI3K/AKT/mTOR signaling pathway according to scientific research. It has been noted that there is an increase in expression in the skin of patients with psoriasis and in a mouse model with psoriasiform symptoms caused by imiquimod[54]. Dysregulation of this pathway has also been associated with types of skin malignancies indicating its importance in skin disorders[55].

The bioactives that collected for grape seed were first checked for ADME properties in Qik Prop module of Schrodinger software where the molecular weight, predicted brain/blood partition coefficient (QPlogBB), Predicted skin permeability (QPlogKp), Human Oral Absorption, Lipinski rule of 5, were observed the bioactives which satisfied all these parameters were selected (Table 7) for network pharmacology and

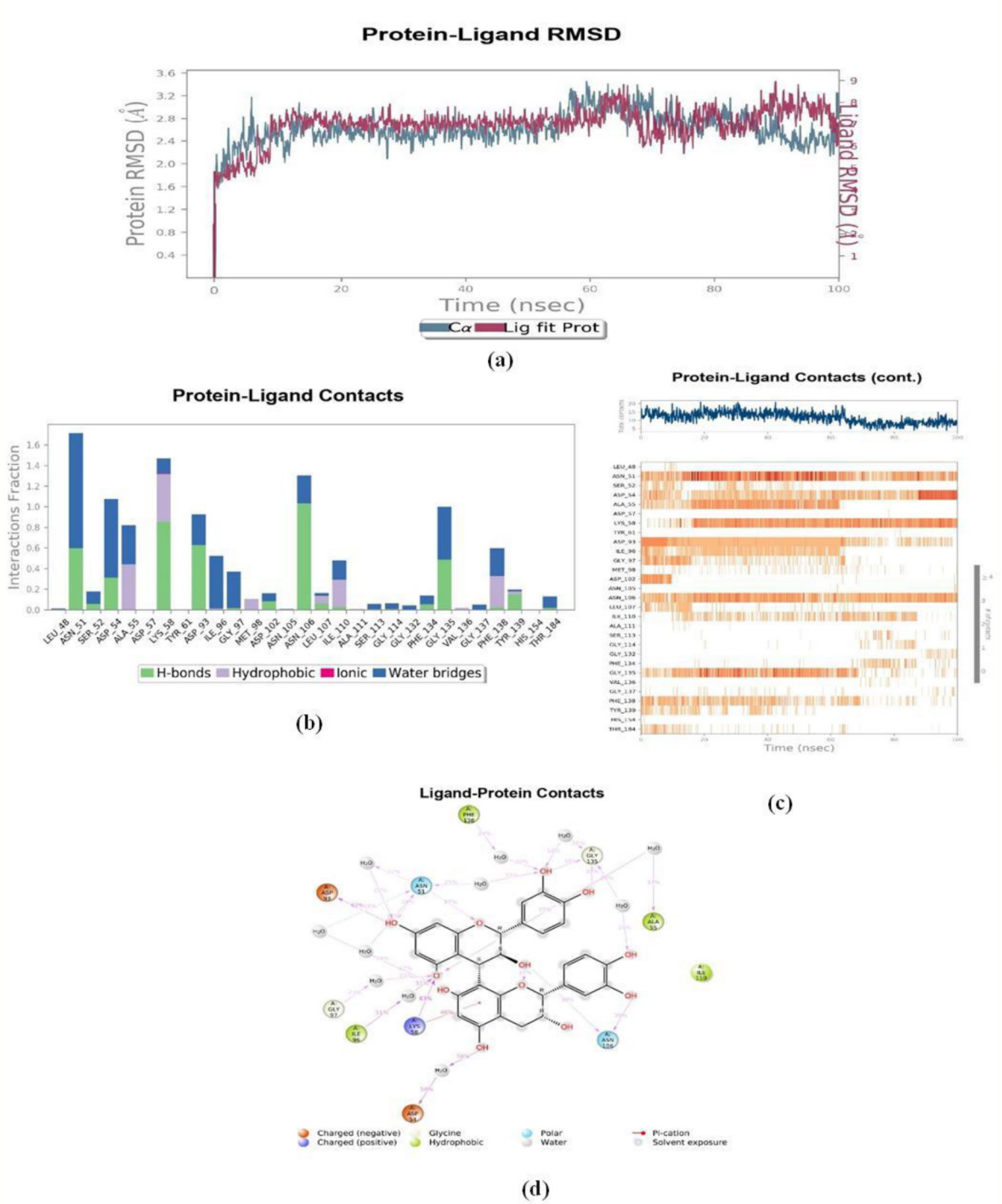


Figure 14. MD Simulation analysis of HSP90AA1-Procyanidin B4. **(a).** Protein (HSP90AA1)-Ligand (Procyanidin B4) RMSD for 100ns. **(b).** Protein-Ligand interaction bonds HSP90AA1 and Procyanidin B4. **(c).** Time of contact of amino acids of the HSP90AA1 to the Procyanidin B4. **(d).** 2D representation of the contacts between the Procyanidin B4 and the HSP90AA1.

molecular docking studies. These parameters can predict whether a drug will be readily absorbed and reach its target in the body, which is essential for its therapeutic effect. Particularly, a lower molecular weight, good skin permeability, and adherence to Lipinski's rule of 5 suggest that the grape seed bioactives with these properties could be promising candidates for the development of effective psoriasis treatments.

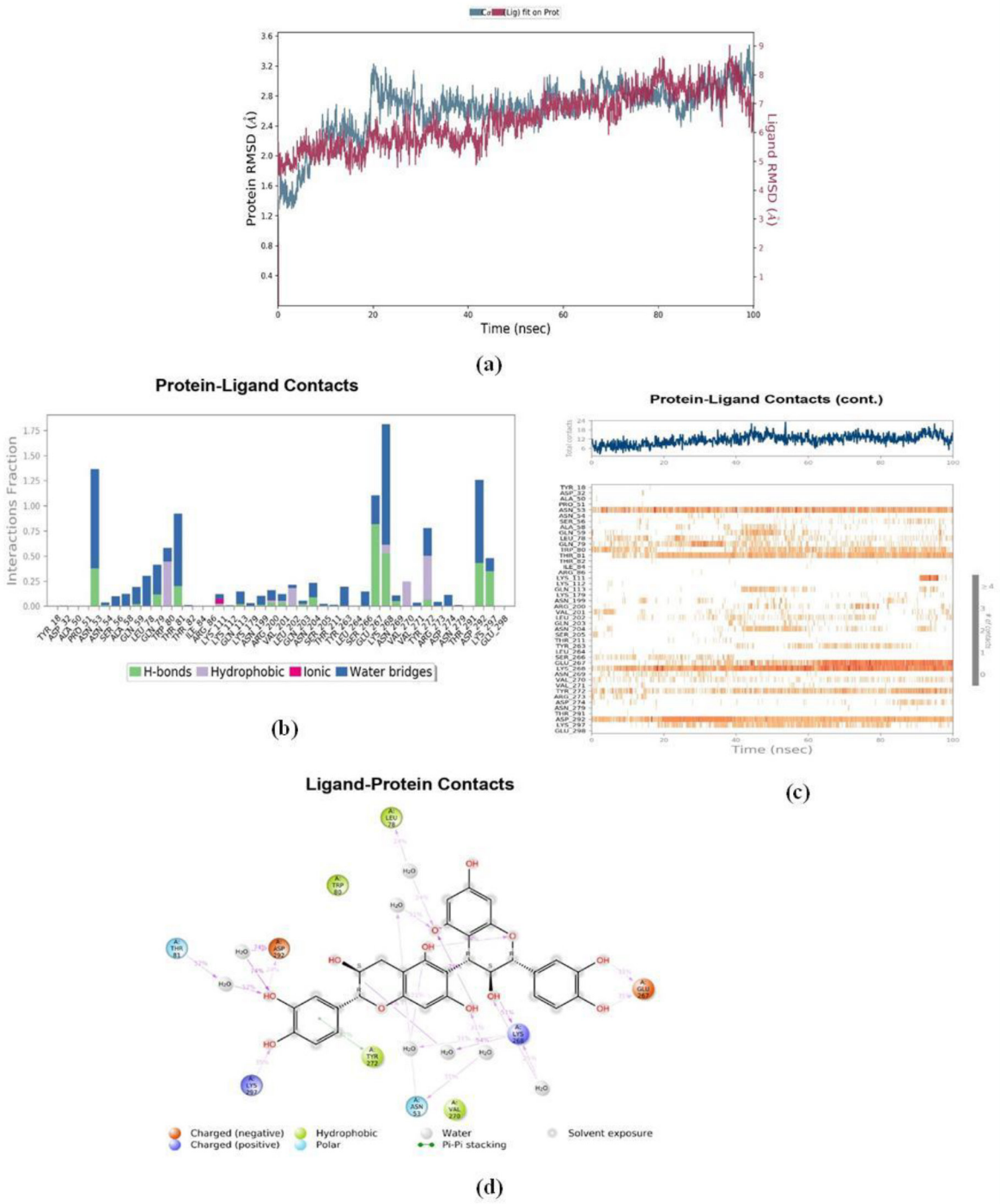


Figure 15. MD Simulation analysis of AKT1-Procyanidin B6. **(a).** Protein (AKT1)-Ligand (Procyanidin B6) RMSD for 100ns. **(b).** Protein-Ligand interaction bonds AKT1 and Procyanidin B6. **(c).** Time of contact of amino acids of the AKT1 to the Procyanidin B6. **(d).** 2D representation of the contacts between the Procyanidin B6 and AKT1.

Thus, these measures can guide the drug development process, and these parameters supports that the bioactive have good bioavailability.

To further explore the potential molecular mechanism of Grape seed in the management of Psoriasis, we performed the molecular docking studies, based on the string PPI degree node proteins, Cytohubba plugin obtained hub proteins, and the KEGG enrichment analysis available degree node proteins all these were observed and searched in PDB

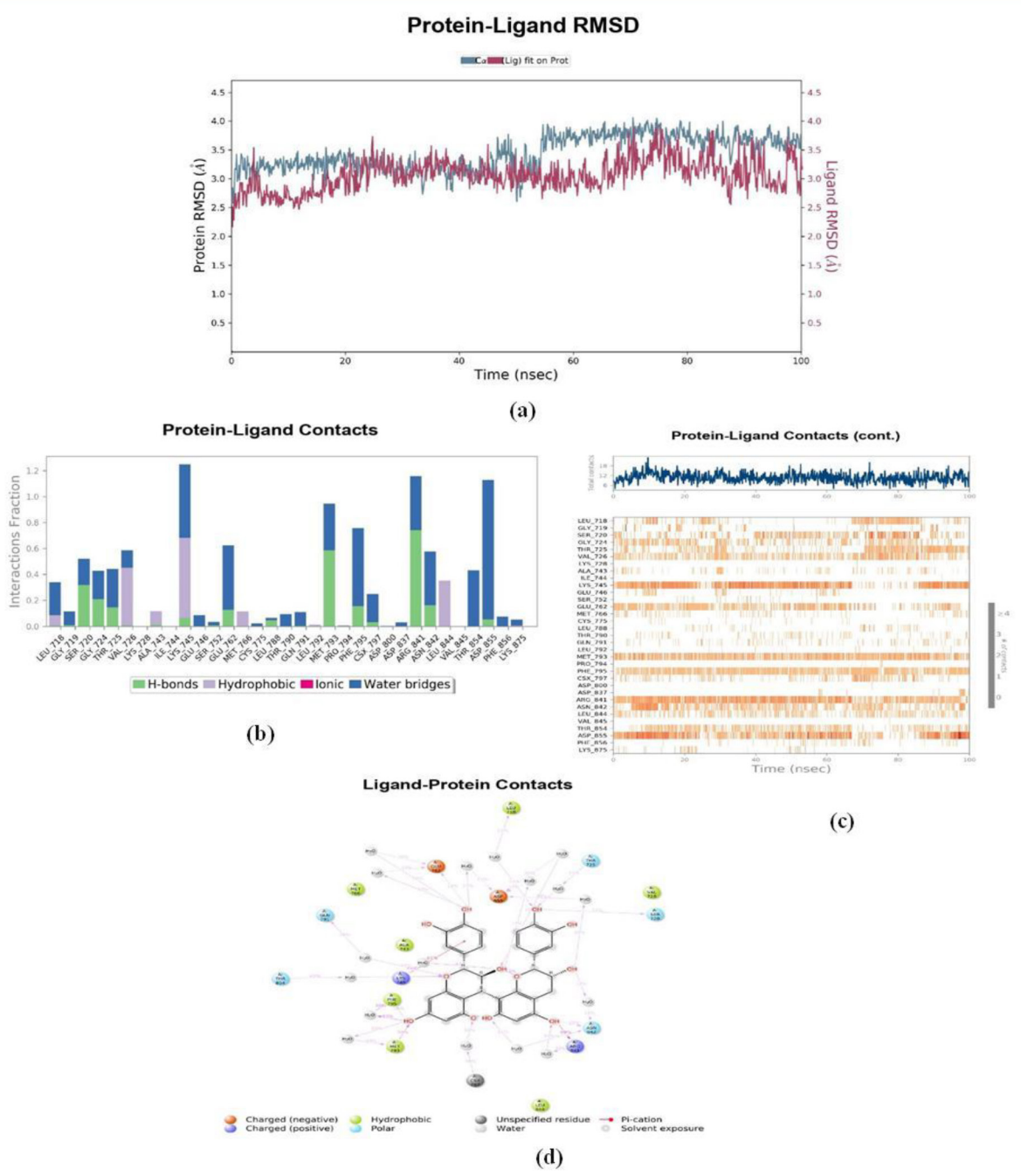


Figure 16. MD Simulation analysis of EGFR-Procyanidin B4. **(a).** Protein (EGFR)-Ligand (Procyanidin B4) RMSD for 100ns. **(b).** Protein-Ligand interaction bonds EGFR and Procyanidin B4. **(c).** Time of contact of amino acids of the EGFR to the Procyanidin B4. **(d).** 2D representation of the contacts between the Procyanidin B4 and EGFR.

database, these proteins were selected based on the criteria of homo sapiens and no mutations and with good RMSD scores (Table 8). Total 8 protein targets were selected and the bioactives that are showed interactions with these proteins were docked in Schrodinger software, the obtained dock scores were all below minus 5 which considered good, docked components. Most of the bioactives have shown good binding scores, but bioactives like Procyanidin B4, Epicatechin-3-gallate, Procyanidin B6, Procyanidin B8 have shown excellent binding scores with proteins like albumin, AKT1, HSP90AA1, EGFR, IGF1R (Figure 8-12). The protein and bioactive dock scores with hydrogen bond interactions and other interactions was mentioned in

(Table 9) where the prominent interactions to observe is hydrogen bonds and the amino acids that formed these bonds were observed, most of the proteins also showed other kind of interactions like Pi-cation, Pi-Pi Stacking etc, and amino acids that participated to form such interactions was also observed. The main criteria to observe is always Hydrogen bonds, later followed by Salt bridges, some components have these salt bridges, because they decide the binding strength that's how good dock scores around 9 to 10 can be obtained. Therefore, it can be inferred that Procyanidin B4, Epicatechin-3-gallate, Procyanidin B6 and Procyanidin B8, the main bioactives of Grape seed, lower oxidative stress and stop the production of inflammatory mediators, like HSP90AA1, AKT1, IGF1R, and EGFR, thus delaying psoriasis progression.

All the protein complexes mentioned had shown better hydrogen bond interactions, the best dock score protein complexes were further selected for MD simulation studies. MD Simulation studies were performed in Schrodinger software Desmond module, three protein complexes with best dock scores HSP90AA1-Procyanidin B4, AKT1-Procyanidin B6, EGFR-Procyanidin B4 were selected. All the three protein complexes had shown good interactions between the protein and the bioactive complex (Figures 14-16). There is compelling evidence that the bioactive compounds found in grape seeds can specifically interact with important proteins involved in the development of psoriasis and have the ability to control the progression of this illness. In the realm of psoriasis, HSP90AA1's involvement has been suggested through its association with the IL-23 and NF-κB pathways, which are identified to be crucial in the progress of psoriasis[56]. AKT1, part of the AKT signaling pathway, plays an essential role in inflammation-mediated diseases like psoriasis[57]. EGFR activation is essential in skin development, wound healing, and keratinocyte proliferation, all processes relevant to psoriasis pathogenesis[58].

Thus, the novel components from the grape seed were recognized based on network pharmacology and molecular docking studies; however, it is crucial to note the limitations of this study. Primarily, while network pharmacology provides a systems-based approach and is an insightful tool in identifying mechanistic pathways, it remains an in-silico approach. Despite the significant insights afforded by network pharmacology and computational methodologies, they come with distinct limitations. The variability in acquired data due to diverse sources and experimental conditions can impact the quality and accuracy of results. This approach is implicitly predictive and thus, proposed interactions need rigorous validation through laboratory assays. The complexity of biological systems and the static nature of these models introduce an added layer of uncertainty. Furthermore, these models may overlook potential off-target effects, meaning they might fail to predict possible adverse reactions. Reliance on bioinformatic algorithms in computational models like molecular docking can also lead to false-positive interactions. Overall, despite these technological advancements, they only provide potential interactions and therapeutic pathways which need further validation, emphasizing the need for an integrative approach pairing *in silico* predictions with meticulous experimental designs. Hence, predicted paths of action and therapeutic potential need to be validated through rigorous *in vitro* and *in vivo* studies, to prove the efficiency of these bioactives on the proteins in psoriasis pathophysiology. By underscoring the potential capabilities of grape seed constituents in modulating disease-linked molecular pathways, this study paves the way for progression towards more targeted and effective treatment strategies for psoriasis.

5. Conclusion

The present study utilized network pharmacology and molecular docking studies to examine the potential mechanism of action of grape seeds in the treatment of psoriasis by constructing a Grape seed bioactive–target Psoriasis-related pathway network (Figure 5). The results showed that grape seed has many different pharmacological effects on psoriasis. These effects include oxidative stress, the inflammatory reaction, and immune system regulation. Our data can serve as a framework for further investigating the mechanism by which Grape seed bioactives exert their therapeutic impact in psoriasis.

Findings revealed key active components, such as Procyanidins B1, B3, B4, and B7, that can act on multiple targets and have anti-inflammatory and immune-modulating properties. In the analysis

of the target network, top proteins such as TNF, AKT1, ALB, IL6, VEGFA, EGFR, MAPK3, STAT3, which are involved in the pathophysiology of psoriasis, were identified as potential targets of grape seed constituents. Results of GO enrichment and KEGG analysis indicated that grape seed may exert its therapeutic action through several pathways including PI3K-AKT signaling pathway, Th17 cell differentiation, and regulation of cytokines, apoptosis, and inflammation. Molecular docking studies further identified bioactive compounds like Procyanidin B4, Epicatechin-3-gallate, Procyanidin B6, and Procyanidin B8 that showed effective binding with proteins such as HSP90AA1, AKT1, and EGFR. These bioactives and protein targets can be novel treatment approach for psoriasis in future and defined mechanism of action can also be predicted through clinical procedures. So, the observed bioactives will show efficacy in controlling the protein targets by PI3K-AKT pathway which are crucial to manage psoriasis pathophysiology. Despite the findings of this *in silico* analysis, it is significant to conduct *in vitro* and *in vivo* studies for validation. Cell line studies can be performed on these protein and bioactive components as *in vitro* studies, further these bioactive components can be tested for their efficacy on the protein targets by using rodent models, which are under the process. Overall, the study illustrates the potential effectiveness of grape seed constituents in the management of psoriasis through their modulation of certain disease-linked molecular pathways and identifies potential targets for more effective therapeutic strategies.

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8. Author Contribution

Vandana Raj Thalathoti: Experimental work, Drafting of research findings; Santh Rani Thakur: Supervision of work. All authors have read and agreed to the published version of the manuscript.

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