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Network pharmacology combined with molecular docking and molecular dynamics to verify the therapeutic potential of mung beans (*Vigna radiata*) against prostate cancer

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Abstract

Background Prostate cancer is the most common oncological disease in men and one of leading causes of death worldwide. Growing evidence has demonstrated the effectiveness of mung bean bioactive compounds in suppressing various cancer cells. However, their effects and underlying mechanisms on prostate cancer have not been verified. The present study aimed to investigate the therapeutical effects and underlying mechanisms of mung bean compounds against prostate cancer.

Results The results revealed that 56 proteins related to prostate cancer could be modulated by mung bean, including several vital proteins of SRC (Sarcoma), Mitogen-Activated Protein Kinase 8 (MAPK8), Heat shock protein 90 kDa alpha member A1 (HSP90AA1), and Harvey Rat sarcoma virus (HRAS). It was also found that the potential pathways associated with prostate cancer pathogenesis comprising pyrimidine metabolism, nitrogen metabolism, and prolactin signaling pathways. Of 19 mung bean compounds docked to four key proteins reveal three promising compound (dulcinoside, peonidin-3-glucoside, and chlorogenic acid) with lower binding affinity score of −7.7, −12.2, −9.0, and −6.5 kcal/mol against SRC, MAPK8, HSP90AA1, and HRAS, respectively in their site of action. Dynamic simulation results also showed values of −36.52 ± 2.93, −35.93 ± 1.67, and −35.77 ± 1.17 kJ/mol for Dulcinoside-SRC, Dulcinoside-MAPK8, and P3G-HSP90AA1 complexes, respectively. The binding of the compound occur in stable and flexible with the proteins. Moreover, all mung bean compounds predicted to have good ADMET properties.

Conclusions The study concluded that dulcinoside, peonidin-3-glucoside, and chlorogenic acid potentially exhibited anticancer activity against prostate cancer in silico. Nevertheless, further studies such as in vitro and in vivo are needed to optimize and prove the efficacy of the mung brand and its compounds against prostate cancer.

Keywords Mung bean, Network pharmacology, Prostate cancer, Molecular docking, Molecular dynamics

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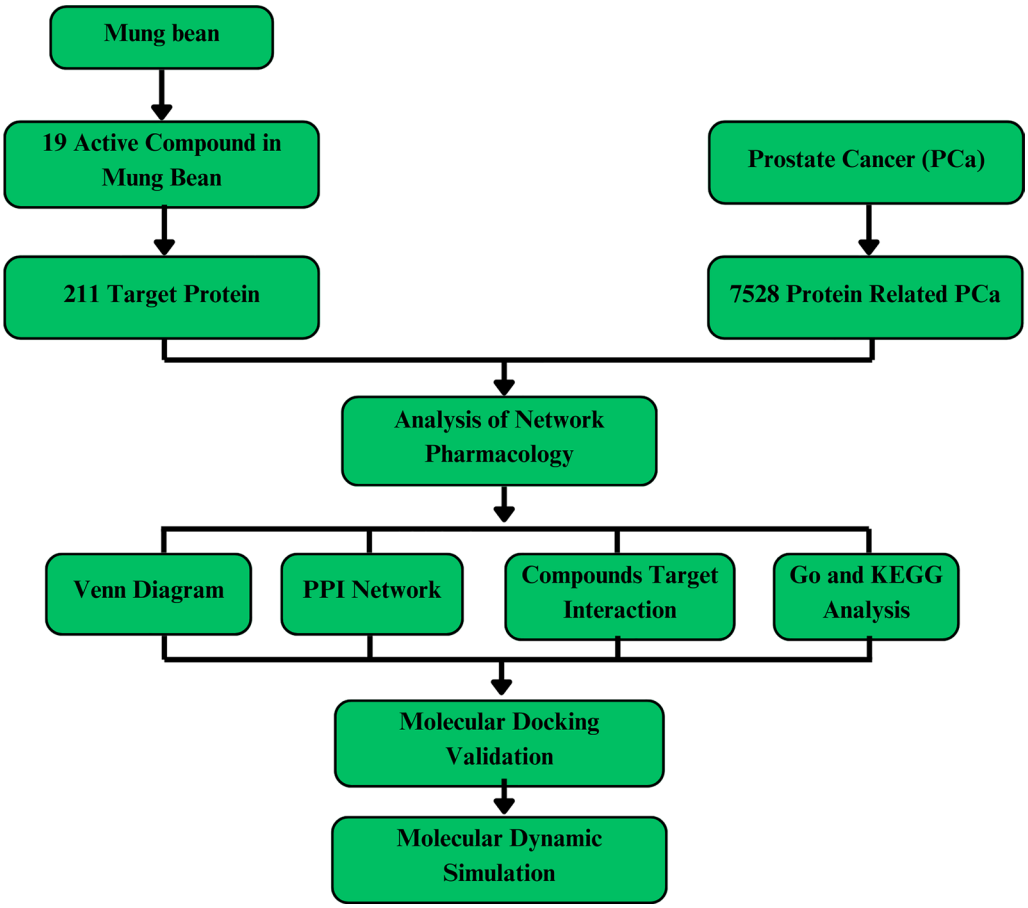
Graphical abstract



1 Background

Prostate cancer is the second most commonly diagnosed cancer in men worldwide after lung cancer. It constitutes significant public health issue as the fifth most frequent cause of cancer-related deaths globally. The various risk factors for prostate cancer are consumption of foods rich in animal saturated fats, red meat, and dairy products, environment, excessive intake of alcohol and coffee, and vitamin D deficiency [1, 2]. The clinical presentation of prostate cancer is associated with decline in the quality of life including sexual, physical, and psychosocial domains [3, 4]. Moreover, the risk of developing cardiovascular diseases and suicide is elevated following a diagnosis of prostate cancer [5].

Bioactive compounds that exert as antioxidants, anti-inflammatory, antilipidemic, and anticancer agents are widely recognized for their beneficial effects on human health. These compounds are predominantly found in fruits and vegetables [6, 7]. In particular, mung bean (*Vigna radiata*) compounds have emerged as promising candidate for anticancer treatments. These plants have demonstrated the ability to confer chemoprotection against breast and cancer cells in vitro and in vivo [8]. The same ability has also been exposed against hepatocarcinoma cancer cells in vitro and in vivo in female BALB/C mice (inbred mice with ability to produce monoclonal antibody) [8].

Mung beans are rich source of flavonoid and phenolic acids, extensively studied for their potential health benefits. Flavonoid compounds of mung bean include anthocyanins, flavanols, flavones, flavonols, and isoflavonoids [9]. In vitro studies have exhibited that anthocyanins can inhibit cell proliferation in the HT29 colon cancer cell line [10]. Flavanol-derived compounds have been found to affect the cell cycle by modulating pathways such as factor-κB, mitogen-activated kinase protein, epidermal growth factor, vascular endothelial growth factor, and matrix metalloproteinase [11, 12].

Besides, flavonol-derived compounds have also been discovered to have anticancer effects by modulating the caspase pathway-3, Bax, and Bcl to induce apoptosis in the PA-1 cell line [7, 11, 13, 14]. Meanwhile, flavone-derived compounds have been investigated for their antineoplastic effects on cell lines of various cancer types, including breast cancer (MCF-7), leukemia (U937), brain tumor (PC12), and esophageal cancer (EC-109) [15, 16].

Phenolic acid compounds in mung beans are hydroxycinnamic acid and hydroxybenzoic acid derivatives and have various health benefits including anticancer effects. Some hydroxycinnamic acid-derived compounds have been uncovered to have cytotoxic effect on cancer cell lines and modulate apoptosis activity [17–19]. Hydroxybenzoic acid derivative compounds have been shown to have similar products to hydroxycinnamic acid derivatives. It modulates the apoptosis process by targeting several proteins such as Bcl-2, caspase-3, and caspase-9. These findings suggest that mung beans can be an anticancer agent [19, 20]. Nevertheless, further research is required to explore these compounds' potential in vivo and better understand their mechanisms.

Despite the ongoing research on prostate cancer, the effects and underlying mechanisms of polyphenol derivates of mung bean on this disease are still inadequately investigated. To uncover, several comprehensive approaches can be adopted such as network pharmacology combined with molecular docking. Besides, molecular dynamics can be considered since these methods have been widely utilized in drug discovery against complex diseases like cancer.

Network pharmacology is scientific method that can help to discover protein-related prostate cancer targeted by mung bean compounds. It is done by merging the fields of bioinformatics, pharmacology, biology, and computer science. Network pharmacology is an innovative analytical approach representing a paradigm shift from the traditional "one-target, one drug" approach to the "network-target, multiple-component therapeutics" approach. It has been considered to assess the effects and underlying mechanisms of diseases since it can provide information on multiple biological processes, metabolic pathways, and drug/compound-target interactions [21, 22].

Furthermore, molecular docking is an established technique that analyzes interactions between drug-like ligands and protein target receptors using computational algorithms. This technique helps to identify suitable active sites, obtain the best geometry, and calculate ligand interaction energies for more effective compound development. Moreover, it can be used to verify the interaction of mung bean polyphenolic compounds with essential prostate cancer proteins and underlined residue and type of binding interaction [23, 24].

Consequently, network pharmacology and molecular docking can be integrated to validate the former and identify affinity bindings. Additionally, molecular dynamic simulations can be used to analyze the interaction stability and flexibility of complexes formed between the active compound of mung bean and critical proteins related to prostate cancer.

Accordingly, this study aimed to analyze the effects and underlying mechanisms of polyphenolic compounds of mung bean on prostate cancer using network pharmacology combined with molecular docking and molecular dynamics. The workflow of the study is presented in Fig. 1.

2 Methods

2.1 Retrieval of polyphenol compounds of mung beans

The literature search revealed 19 different polyphenol compounds of mung bean (*Vigna radiata*) that were included in this study. They were cyanidin-3-glucoside, peonidin-3-glucoside, pelargonidin-3-glucoside, quercetin, myricetin, kaempferol, catechin, vitexin, isovitexin, luteolin, dulcinoside, p-coumaric acid, caffeic acid, ferulic acid, chlorogenic acid, and sinapic acid, gallic acid, syringic, and gentisic acid [8, 9, 25].

2.2 Analysis of protein related polyphenol compounds of mung bean and Prostate cancer

The targets of polyphenol compounds mung bean were determine using two integrative online based tools, SwissTargetPrediction and PharmMapper by employing SMILES and SDF file of the compounds. SwissTargetPrediction was set in default mode. Meanwhile, PharmMapper was adjusted to "HumanOnly" and the selection targets were conduct by z-score value of > 1.5. The retrieved protein were merged and the duplicate is removed.

Furthermore, the searching for protein-related prostate cancer was conducted using two different databases, including GeneCards and Online Mendelian Inheritance in Man (OMIM) with the keyword "Prostate Cancer". The results of protein analysis were merged and the duplicate is removed.[26].

Afterward, the collected target of mung bean compounds were analyzed and intersected with prostate cancer related protein using Venny 2.1.0. Identified overlapped protein assumed as core target of mung bean in prostate cancer [27].

2.3 Construction of protein–protein interaction network

The STRING database were used to construct protein–protein interactions (PPI) network for intersecting

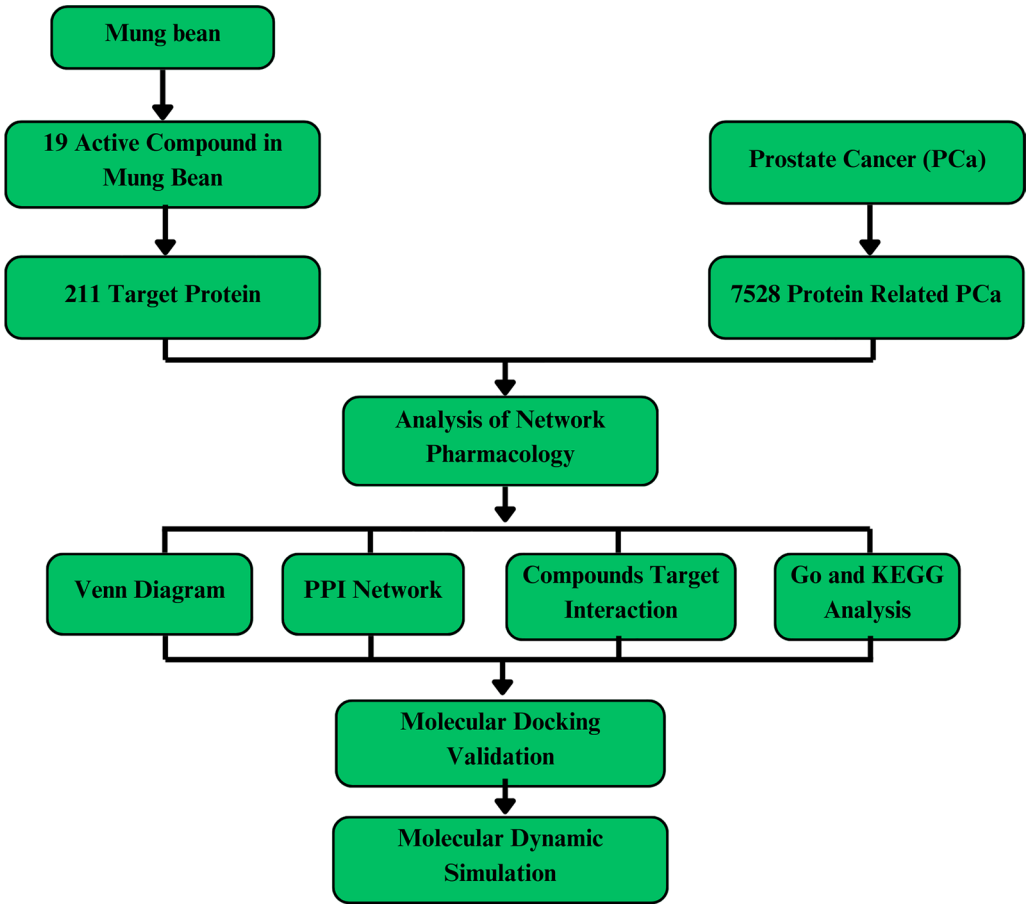


Fig. 1 Workflow of network pharmacology combine with molecular docking and dynamic stimulation to verify therapeutic potential of mung bean against prostate cancer

proteins in previous section. To ensure robustness results, the screening threshold of the tools were set in confidence level > 0.9 with "Homo Sapiens" mode. Furthermore, the PPI was visualized and analyzed in Cytoscape 3.9.1 and the free proteins (proteins that are not bound to the main network) were removed [27].

2.4 Analysis of topological network and screening of key targets

Analysis of topological protein was computed by utilizing the cytoscape plug in, CytoNCA. In this analysis, we use four different centrality including degree (DC), betweenness (BC), eigenvector (EC), and closeness centrality (CC). The higher node score indicated to have a crucial role within the PPI network. Furthermore, The main target protein is analyzed from the 10 proteins with the highest value in each of the four centrality (DC, BC, EC and CC) which then intersected in ven diagram to obtain the main protein [28].

2.5 Gene ontology enrichment and KEGG signal pathway analysis

Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway annotation were performed by ShinyGO v 0.77 with specified organism "*Homo Sapiens*". GO and KEGG pathway analysis was conducted to examine the protein cluster within the network in their influence on enriched biological process (BP), molecular function (MF), cellular component (CC) and pathway related prostate cancer. The cut-off FDR were set below 0.05 to obtain the top 10 GO annotation and KEGG pathrway lollipop plot [29].

2.6 Molecular docking analysis

Molecular docking analysis was conducted to assess the ability of the mung bean compounds to bind with screened key proteins of prostate cancer. The docking was carried out by AutoDock Vina program package. The selected compound of mung bean as well as Docetaxel and Bicalutamide (as positif control drug of prostate

cancer) were retrieved from the PubChem database and further prepare using Marvin View and autodock into. pdbqt format. Meanwhile, the key protein including SRC (PDBID: 1O4N), MAPK8 (PDBID: 4L7F), HSP90AA1 (PDBID: 1OSF), and HRAS (PDBID: 4DLS), were obtained from Research Collaboratory for Structural Bioinformation Protein Data Bank (RCSB PDB). The protein wre further prepare using BIOVIA Discovery Studio Visualizer and autodock to obtaind.pdbqt format of the proteins. Prior docking, we also determine the grid box parameters to ensure docking of compound with selected protein occure in catalytic site. All docking were conduct by AutoDock Tools 1.5.6 and the results were visualized by BIOVIA Discovery Studio Visualizer 2021 to display the 2D and 3D structure [28]

2.7 Prediction of ADMET and drug likeliness profiles of mung bean compounds

The ADMET prediction was conducted to determine absorption, distribution, metabolism, excretion and toxicity of the compounds. The prediction was completed by pkCSM (https://biosig.lab.uq.edu.au/pkcsm/), SwissADME (http://www.swissadme.ch/index. php), and admetSAR (http://lmmd.ecust.edu.cn/admetsar2/).

2.8 Dynamic simulation and calculation of

Molecular dynamics of proteins with ligands were performed via OpenMM and AMBER force fields run in Google Colab. The temperature was set constant at 310 K. and a time step of 2 fs.

3 Result

3.1 Potential targets of mung bean compounds in prostate cancer

The potential targets of mung bean (*Vigna radiata*) compounds were analyzed using PharmMapper and SwissPrediction tools. After assessing the database and removing duplicate targets, 211 proteins targeted by mung bean compounds were obtained. Meanwhile, after searching GeneCard and OMIM databases and removing repeated proteins, 7.528 prostate cancer-related proteins were achieved. Furthermore, both groups of proteins (drug and disease) were intersected using Venn diagrams (Venny 2.1.0). It provided 159 overlapping proteins that were considered potential targets of mung bean compounds in prostate cancer therapy (Fig. 2).

4 Network contruction, topological analysis and key protein screening

Next, 159 prostate cancer proteins targeted by mung bean compounds were further examined to determine the interaction of these proteins network and topological analysis. The protein protein interaction were buid using online based tools STRING and Cytoscape software package. The results of PPI displayed in Fig. 3a indicated that some of the proteins had no interaction with others and those in the main cluster network that further were removed using Cytoscape. The final network results 56 nodes proteins with 121 edges protein protein interaction (Fig. 3b). Furthermore, analysis of topological network were conduct using CytoNCA (cytoscape plug in) provide different score in four different centrality

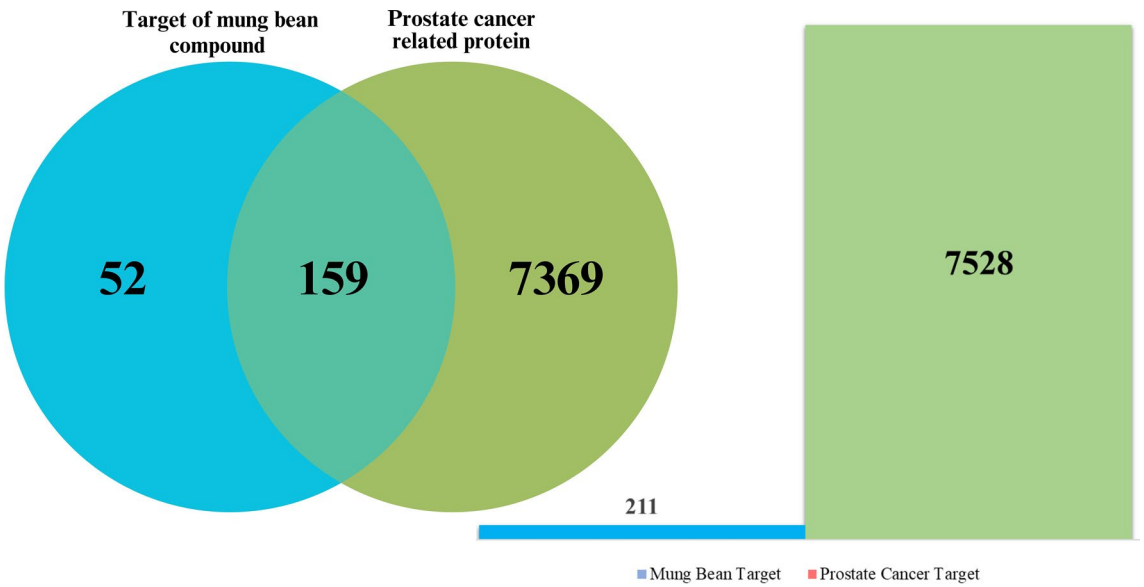


Fig. 2 Venn Diagram Analysis Intersection of Prostate cancer related protein with mung bean compound target

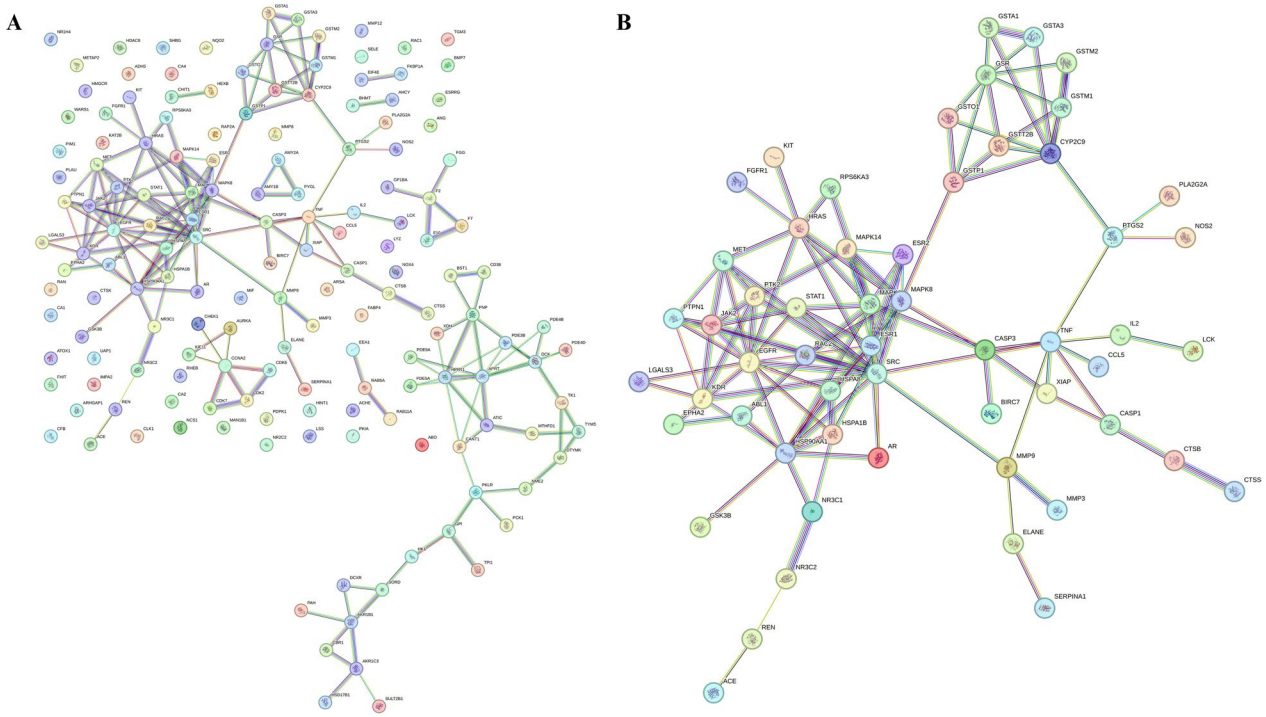


Fig. 3 Protein–Protein Interaction network of mung bean compound target in prostate cancer. **A** The PPI Network of 159 protein target of mung bean compound target in prostate cancer therapy according to STRING. **B** The PPI Network of 56 protein target of mung bean compound target in prostate cancer therapy after clearing non interaction protein with main network

including degree (DC), betweenness (BC), eigenvector (EC), and closeness centrality (CC). The higher node score indicated to have a crucial role within the PPI network (Table 1). Menggunakan plug in dan centrality yang sama, key protein screening dilakukan untuk memperoleh putative and most potential protein in prostate cancer that targeted by mung bean compound. Top 10 protein pada masing masing sentrality were retrieved and further intersected by venn diagram (Fig. 4A–D). This analysis revealed four potential proteins in the interaction such as SRC, MAPK8, HSP90AA1, and HRAS and suggested as key protein (4E). The proteins obtained were further constructed on the Drug–Compound–Target–Disease Network to make the final visualization in the form of network pharmacology (Fig. 5).

4.1 GO enrichment and KEGG signal pathway analysis

Gene Ontology analysis was performed to analyze molecular function, cellular components, and biological processes associated with prostate cancer targeted by mung bean compounds. It aimed to predict comprehensive picture of the changes in molecular functions, cellular components, and biological processes that occur in prostate cancer when mung bean compounds were challenged into the disease. There were 468 molecular functions and several essential ones found, namely glutathione transferase activity and MAP kinase activity. Meanwhile, 200 cellular components related to the input protein were also uncovered. Some important cellular features included the ficolin-1-rich granule lumen and endosome lumen. Another finding was that the proteins involved 1000 biological processes, including the glutathione derivative metabolic process and cyclooxygenase pathway. KEGG was conducted to analyze the pathway mainly enriched in prostate cancer-related proteins targeted by mung bean compounds. In this analysis, 206 pathways involved in 56 proteins inputted were uncovered. Several critical protein-related pathways comprise prostate cancer, pyrimidine metabolism, nitrogen metabolism, and prolactin signaling pathways. The top 10 items were then ranked based on the number of annotations to functional area (Fig. 6a–d).

4.2 Molecular docking

The 19 compounds were docked with primary potential targets, including SRC, MAPK8, HSP90AA1, and HRAS, to verify the therapeutic potential of mung mean compounds. They included cyanidin-3-glucoside, peonidin-3-glucoside, pelargonidin-3-glucoside, quercetin, myricetin, kaempferol, catechin, vitexin, isovitexin, luteolin, dulcinoside, p-coumaric acid, caffeic acid, ferulic acid, chlorogenic acid, and sinapic acid, gallic acid, syringic,

Table 1 Topological of protein rated prostate cancer targeted by mung bean polyphenol compounds

No.	Name	Degree	Eigenvector	Betweenness	Closeness
1	SRC	17	0.426647450	1107.8293	0.46218488
2	EGFR	13	0.332915280	269.2231	0.37414965
3	HSP90AA1	11	0.264402800	449.6303	0.37671232
4	MAPK8	10	0.229519040	698.9374	0.41666666
5	MAPK1	10	0.254034370	171.2896	0.37162160
6	ESR1	10	0.298669550	86.1120	0.39007092
7	HRAS	8	0.199874040	287.6199	0.37414965
8	CYP2C9	8	0.008902299	347.6158	0.30054644
9	TNF	8	0.082636690	963.3317	0.41353384
10	GSR	7	0.007335343	120.2747	0.26442307
11	JAK2	7	0.218346700	4.7190	0.33950618
12	KDR	6	0.172847000	44.7571	0.34810126
13	PTK2	6	0.192907650	16.0119	0.33742332
14	MET	6	0.198975440	7.9000	0.34375000
15	ESR2	5	0.174863140	7.4212	0.35714287
16	MAPK14	5	0.148203310	16.2521	0.32544377
17	PTPN1	5	0.173795660	1.1190	0.33333334
18	STAT1	5	0.197163760	4.9541	0.34161490
19	HSPA8	5	0.162360920	20.8701	0.34161490
20	HSPA1B	5	0.134206980	150.9034	0.34810126
21	GSTP1	5	0.033326443	506.9938	0.33536586
22	CASP3	5	0.077068200	199.9538	0.36184210
23	MMP9	4	0.067870386	316.0000	0.36912750
24	GSTM1	4	0.003264759	3.2984	0.23605150
25	PTGS2	4	0.012179226	423.4212	0.33333334
26	GSTT2B	4	0.006795823	22.9468	0.27363184
27	RAC2	4	0.124527020	54.4196	0.35947713
28	NR3C1	3	0.052319724	312.0000	0.30054644
29	GSTA1	3	0.002379821	2.6317	0.23504274
30	GSTO1	3	0.006378370	2.6317	0.27227724
31	GSTM2	3	0.002493218	2.6317	0.23504274
32	GSTA3	3	0.002379821	2.6317	0.23504274
33	XIAP	3	0.022363890	17.1333	0.31609195
34	CASP1	3	0.013746372	212.0000	0.30219780
35	AR	3	0.127591100	0.0000	0.33950618
36	ABL1	3	0.056662920	15.4055	0.29569890
37	NR3C2	2	0.006856060	212.0000	0.23605150
38	IL2	2	0.010818483	108.0000	0.29729730
39	RPS6KA3	2	0.058497634	0.0000	0.29729730
40	ELANE	2	0.008891501	108.0000	0.27363184
41	LGALS3	2	0.065095630	0.6190	0.27638190
42	CTSB	2	0.001800137	108.0000	0.23504274
43	REN	2	0.000904500	108.0000	0.19298245
44	EPHA2	2	0.050144285	4.5095	0.27777780
45	PLA2G2A	1	0.001566955	0.0000	0.25114155
46	NOS2	1	0.001566955	0.0000	0.25114155
47	MMP3	1	0.008744317	0.0000	0.27093595
48	LCK	1	0.001392792	0.0000	0.23012552
49	KIT	1	0.025786007	0.0000	0.27363184
50	GSK3B	1	0.034113500	0.0000	0.27500000
51	FGFR1	1	0.025786007	0.0000	0.27363184
52	SERPINA1	1	0.001143476	0.0000	0.21568628
53	CTSS	1	0.000230740	0.0000	0.19097222
54	CCL5	1	0.010639674	0.0000	0.29411766
55	BIRC7	1	0.009953668	0.0000	0.26699030
56	ACE	1	0.000116643	0.0000	0.16224189

and gentisic acid. The validation was performed using molecular docking. It is shown that all compound could interact with the proteins. Dulcinoside become compound with the lowest docking score against SRC targets ($\Delta G = -7.7$ kcal/mol) and MAPK8 ($\Delta G = -12.2$ kcal/mol) (Fig. 7). Meanwhile, P3G possessed the lowest value against the HSP90AA1 target ($\Delta G = -9.0$ kcal/mol) and luteolin on HRAS ($\Delta G = -7.2$ kcal/mol) (Fig. 8 and Table 2.) Although luteolin was docked on a non-active site, chlorogenic acid was chosen for further investigation of residue interactions. In addition, the three compounds (dulcinoside, peonidin-3-glucoside, and chlorogenic acid) involved had better binding values than the controls. Furthermore, as presented in Table 3, several interactions occurred in the compounds and target bonds, namely hydrogen bonds, Van der walls, Pi–Pi T-Shaped/Pi–Sigma, Unfavorable bump, Carbon Hydrogen Bond, Pi–Sulfur/Sulfur–X interaction, Pi–Cation, Alkyl/Pi–Alkyl Interaction, and Halogen bonds.

4.3 Prediction of ADMET and drug likeliness profiles of mung bean compounds

ADMET prediction were essential aspects of drug discovery. In this study, three different tools including pkCSM, SwissADME, and admetSAR, were employed since they can accurately predict the ADME and toxicity of the compounds/drugs. The results exhibited that the values of intestinal absorption of the test compounds were relatively lower than that of the positive control. Although the skin permeability of all test compounds had a more negative value of logKp than the control, they had poor skin permeability compared to the control. Each test compound was not permeable to Caco2 and had no P-gp substrate or inhibitor. The Volume Distribution steady state (VDss) values of all test compounds had better deals, and only peonidin-3-glucoside had subcellular localization in the nucleus, while others did in the mitochondria (Table 4). Compared to the positive control, all test compounds were poor in blood–brain barrier permeability. The test

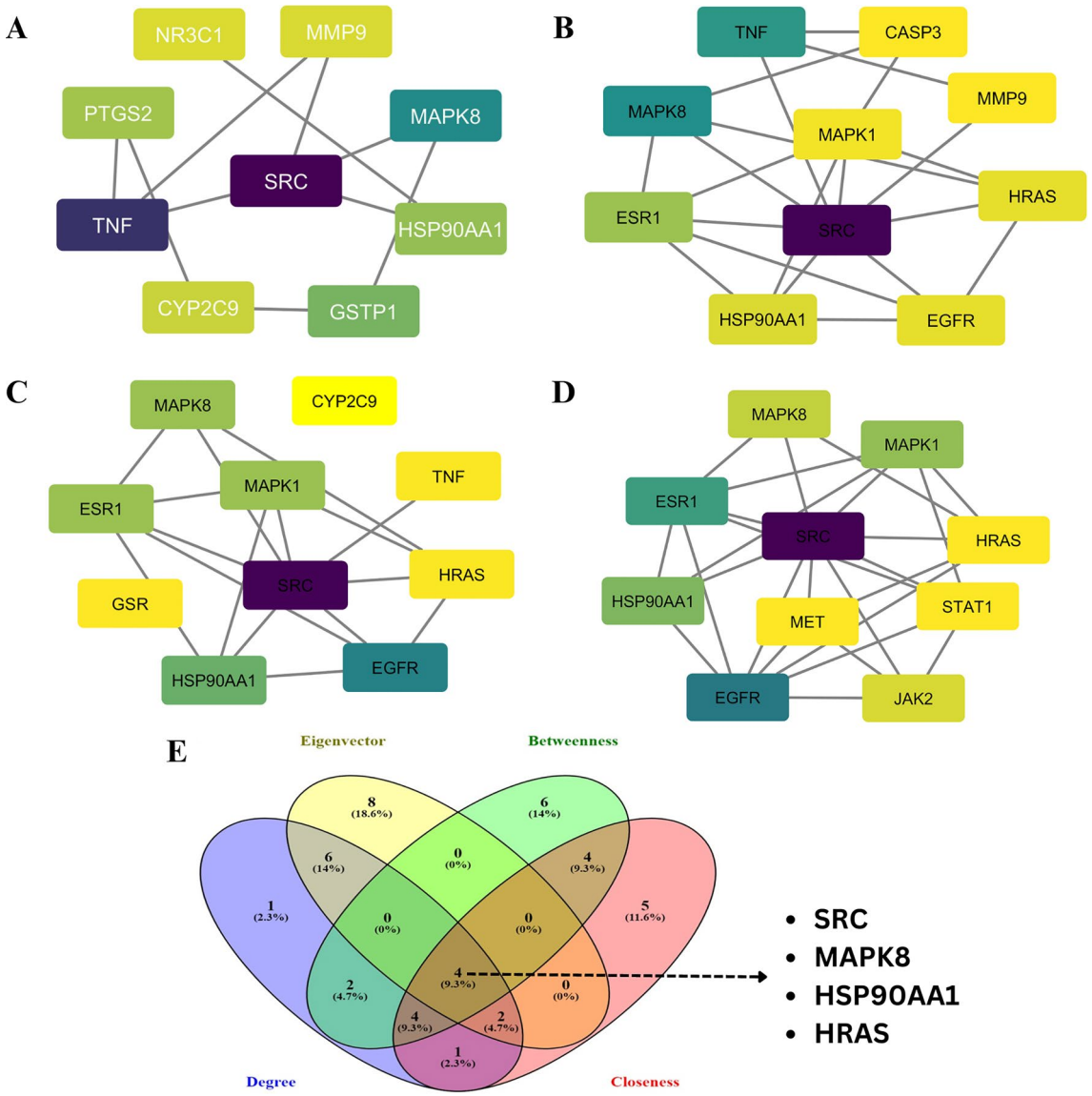


Fig. 4 Top 10 potential target protein in different centrality based on highest score. **A** Betweenness **B** Closeness **C** Degree **D** Eigenvector **E** Venn diagram of top 10 proteins that figurize four obtained key proteins including SRC, MAPK8, HSP90AA1, and HRAS

compounds could not inhibit cytochrome and were not a substrate of the cytochrome. In addition, none of the compounds that predicted hepatotoxic, carcinogenic, and toxic to the AMES model (Table 5). All three compounds violate Lipinski's rule. Dulcinoside had a significant molecular weight, hydrogen acceptor of > 10, and hydrogen donor of > 5. Meanwhile, peonidin had a hydrogen acceptor of > 10 and a hydrogen donor of > 5. Finally, chlorogenic acid had hydrogen donor > 5 (Table 6).

4.4 Molecular dynamic and binding free energy

The stability and dynamic of ligand–protein interaction in top ligand–protein complexes were further observed. Molecular dynamics were simulated for 5 ns to analyze root mean square deviation (RMSD), root mean square fluctuation (RMSF), and Radius of Gyration (RoG). Based on Fig. 9a–d, the RMSD values of three compound-receptor complexes, including Dulcinoside-SRC, Dulcinoside-MAPK8, and P3G-HSP90AA1, fluctuated and were less than 2.5 Å. It indicates that the binding was

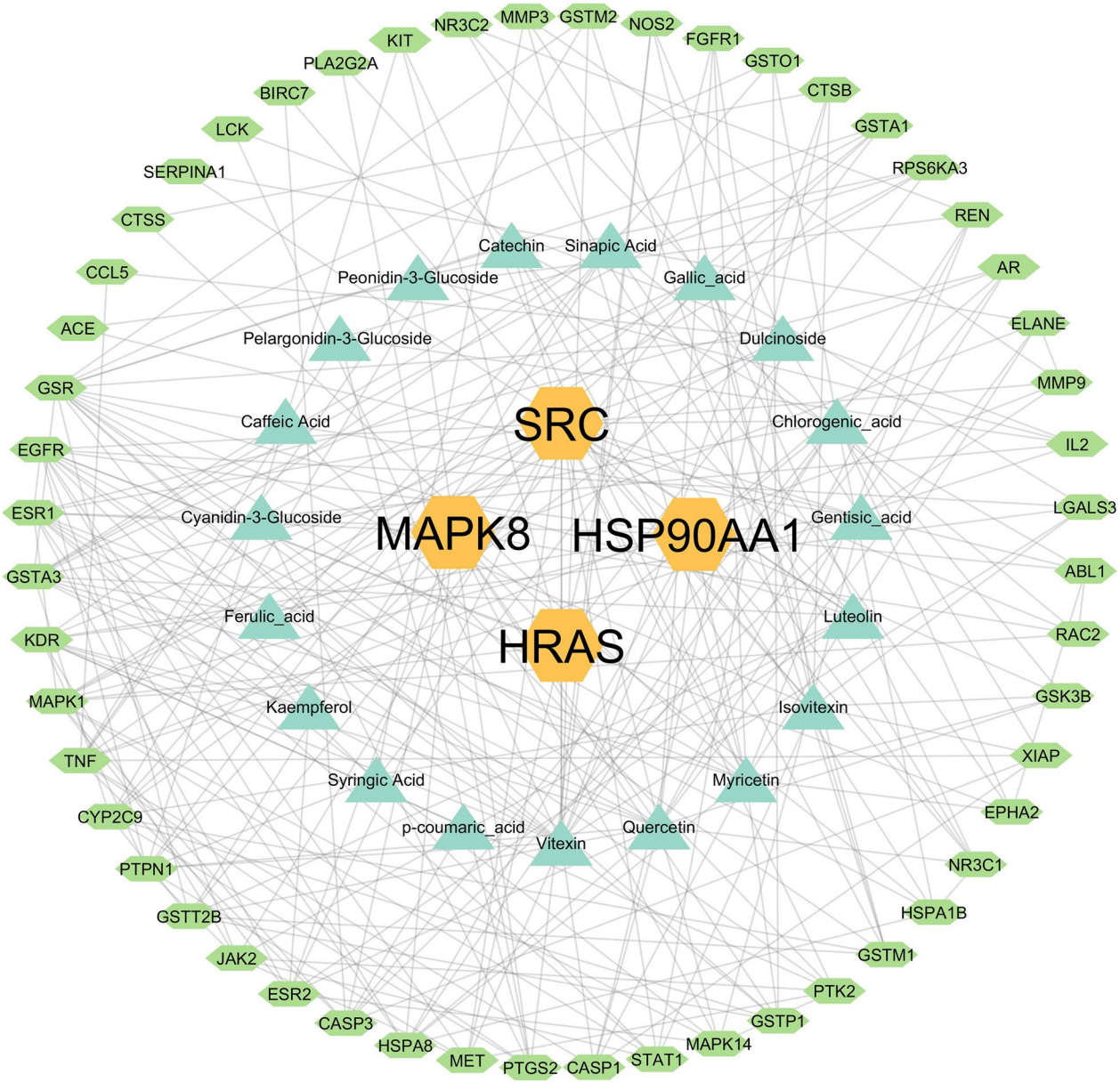


Fig. 5 Drug–Compound–Target–Disease Network with 4 potential key protein

relatively stable. Based on Fig. 8a, the RMSD of the Dulcinoside-SRC interaction was stable at 3 ns initially, then increased at 3.5 ns, and finally stable at 4–5 ns, indicating it reached equilibrium. Meanwhile, the equilibrium phase of the Dulcinoside-MAPK8 interaction was predicted in 3–5 ns. In contrast to the three complexes, the chlorogenic acid-HRAS interaction demonstrated abnormal fluctuations with RMSD values ranging from 0.5 to 6 Å.

Additionally, in line with RMSD, the RMSF values of three compound-receptor complexes, including Dulcinoside with SRC, Dulcinoside with MAPK8, and Peonidin-3-glucoside with HSP90AA1, demonstrated good fluctuations and indications of stable interactions since the values ranging from 0.5 to 6.0 Å. With the exception of chlorogenic acid-HRAS, the 170 amino acid residue obtained an RMSF value of about 30 Å. Other outputs from the molecular dynamic (Fig. 9a–d) were RoG values ranging from 13.05–13.40 Å (Dulcinoside-SRC), 22.1–22.7 Å (Dulcinoside-MAPK8), 16.9–17.4 Å (Peonidin-3-glucoside -HSP90AA1), and 14.8–15.3 Å (chlorogenic acid-HRAS). RoG value measures how compact the protein is with the ligand molecule. The figures

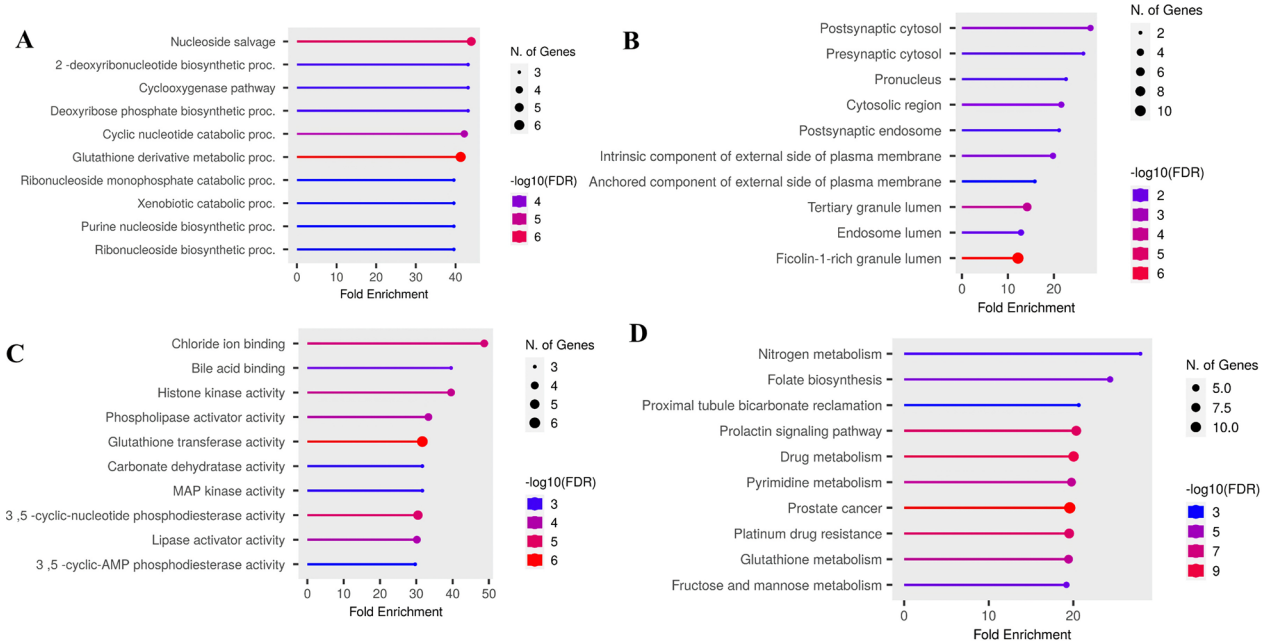


Fig. 6 Functional annotation and KEGG pathway enrichment analysis of 56 core prostate cancer targets of mung bean compound. **A** Top 10 of Biological Process. **B** Top 10 of cellular component. **C** Top 10 of molecular function. **D** Top 10 of KEGG pathways

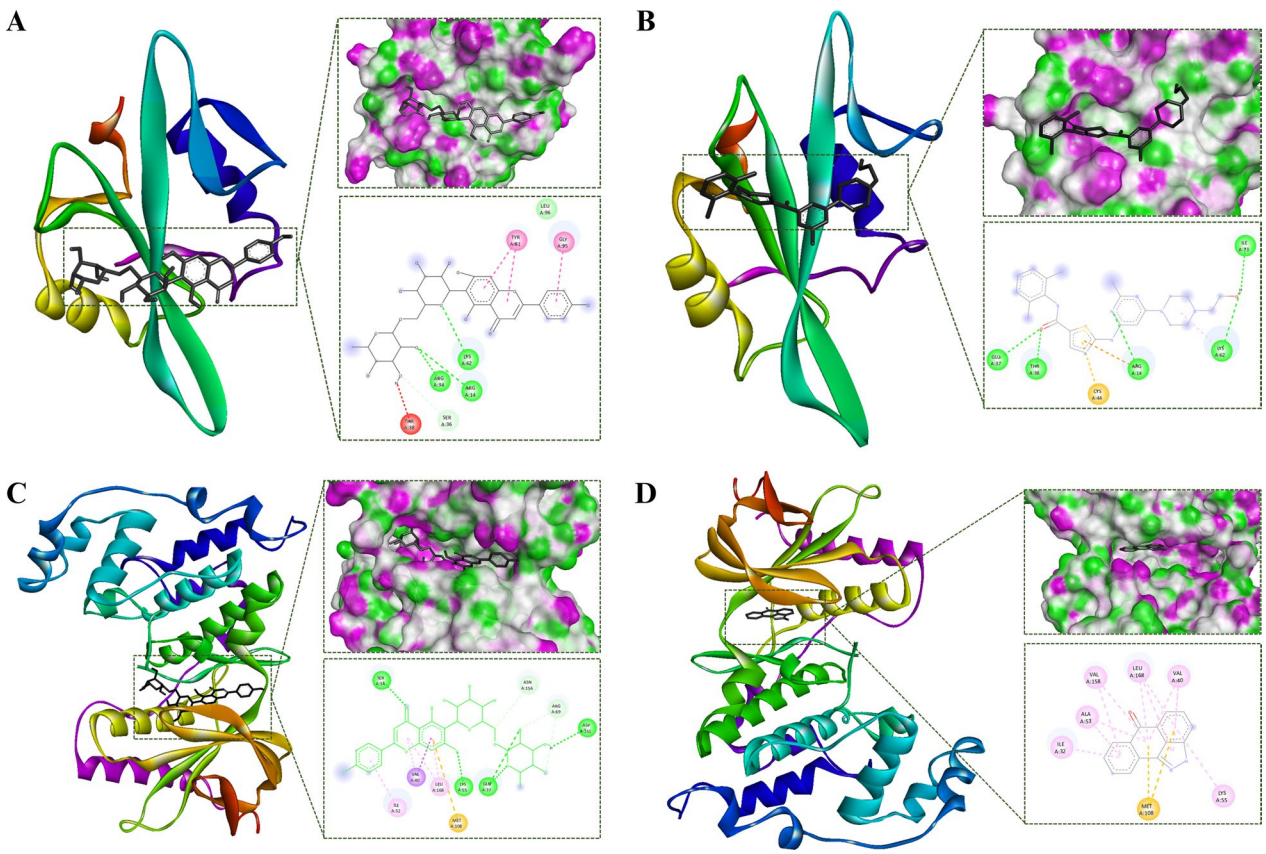


Fig. 7 Visualization of 2D and 3D of molecular docking results of best protein–ligand (mung bean compound and positive control) complexes **A**. SRC-Dulcinoside **B** SRC-Dasatinib (control) **C** MAPK8-Dulcinoside **D** MAPK8-Pyrazolanthrone (control)

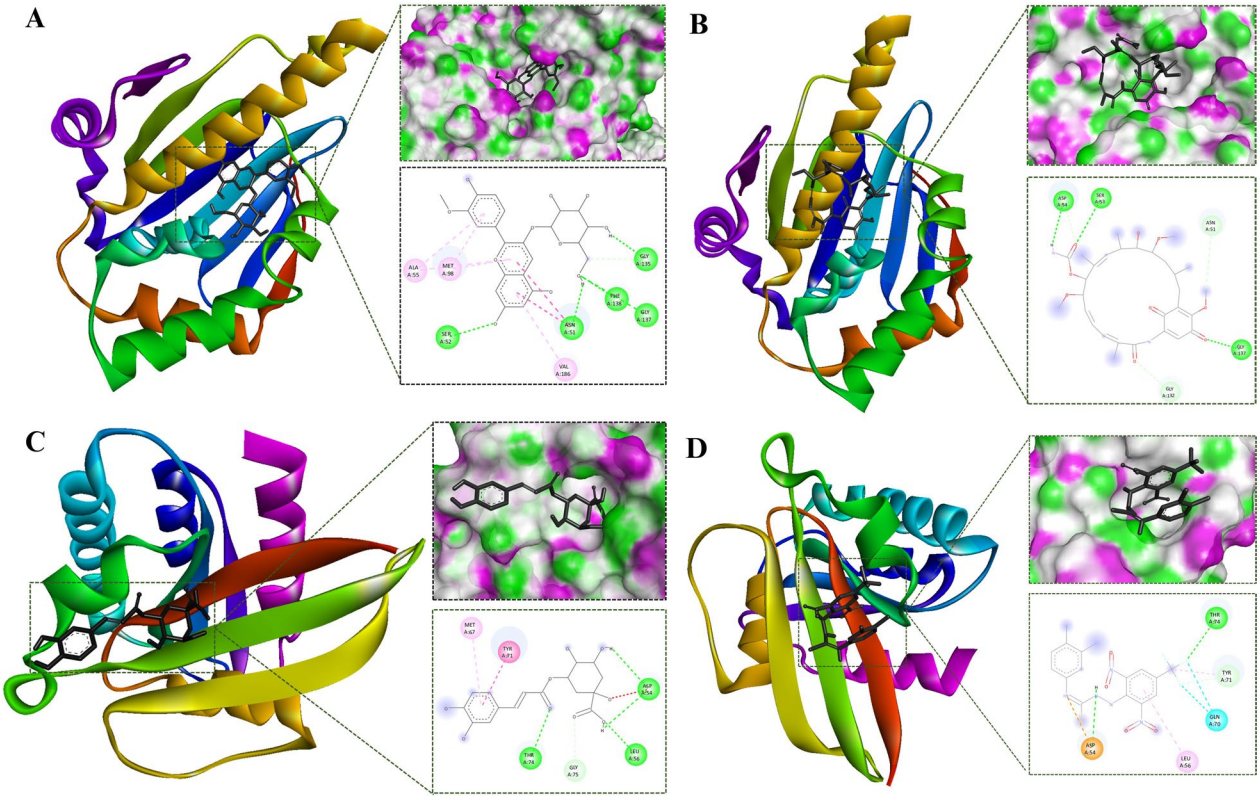


Fig. 8 Visualization of 2D and 3D of molecular docking results of best protein–ligand (mung bean compound and positive control) complexes **A** HSP90AA1-P3G **B** HSP90AA1-Geldanamycin (control) **C** HRAS-ChlorogenicAcid **D** HRAS-Kobe0065 (control)

show that the gyrase values were stable, and no sudden change in RoG values existed. The values indicate that the binding of protein with ligand occurs very compactly.

Furthermore, we also found that the average binding free energy (ΔG) of three receptors-ligand complexes, including Dulcinoside-SRC, Dulcinoside-MAPK8, and P3G-HSP90AA1, exhibited almost the same values of -36.5187 ± 2.93, -35.93 ± 1.67, and -35.7723 ± 1.17 kJ/mol, respectively. Meanwhile, the chlorogenic acid-HRAS interaction produced a binding free energy of -12.5533 ± 1.65 kJ/mol (Table 7).

5 Discussion

Recently, drug discovery and development have entered new era with the concept of going back to nature. The concept is realized through natural product-based compound approach that has been proven effective in curing various diseases, including prostate cancer. Among these, several compounds have been suggested to provide anticancer activity against prostate cancer [30]. Mung bean contains many bioactive compounds that can potentially be used as cancer drugs, such as flavonoid, alkaloid, and tannin derivatives compounds [8, 9, 25].

This study comprehensively explained the effects of the mung bean compounds on prostate cancer and the essential proteins and pathways by applying a network pharmacology approach. Furthermore, this study also verified the underlying mechanisms using molecular docking dynamics and investigated the binding free energy with the MM/GBSA approach.

Network pharmacology was conducted to understand the interaction of each compound with its biological targets to provide information on potential targets that play role in prostate cancer progression [22]. The analysis found that there were 56 main protein targets associated with prostate cancer. Further network analysis specifically uncovered four key potential targets, including SRC, MAPK8, HSP90AA1, and HRAS. Conversely, functional enrichment analysis discovered the 56 proteins associated with various biological, molecular, and pathway processes linked to prostate cancer. As a result, GO enrichment found that these proteins could involve molecular function in prostate cancer. Two essential pathways in the pathogenesis of prostate cancer comprised glutathione transferase activity and MAPK activity. The MAPK pathway contributes to prostate cancer progression, where p38,

Table 2 The docking result of key protein target with mung bean compound and positive control

	SRC (Dasatinib)	MAPK8 (Pyrazolanthrone)	HSP90AA1 (Geldanamycin)	HRAS (Kobe0065)
Control	−6.4	−9.6	−6.4	−5.7
Docetaxel	−6.3	−8.7	−6.8	−5.4
Bicalutamide	−6.3	−9.2	−8.4	−5.4
Compound				
Caffeic acid	−5.1	−7.0	−6.1	−5.2
Catechin	−5.9	−9.0	−7.7	−5.9
Chlorogenic acid	−6.3	−9.4	−7.3	−6.5
Cyanidin 3 glucoside	−6.7	−9.0	−8.9	−6.4
Dulcinoside	−7.7	−12.2	−8.7	−6.1
Ferulic acid	−4.9	−6.9	−5.4	−5.3
Gallic acid	−5.4	−5.9	−5.6	−4.9
Gentisic acid	−5.1	−5.9	−5.4	−6.4
Isovitexin	−6.6	−10.7	−7.9	−6.7
Kaempferol	−5.6	−9.1	−7.5	−5.9
Luteolin	−6.2	−9.4	−8.1	−7.2
Myricetin	−5.9	−9.3	−8.3	−5.9
Pelargonidin-3-glucoside	−6.0	−9.0	−8.9	−6.2
Peonidin-3-glucoside	−6.1	−9.1	−9.0	−6.1
p coumaric acid	−4.8	−6.5	−5.4	−5.2
Quercetin	−6.3	−9.5	−8.1	−6.0
Sinapic acid	−4.5	−7.0	−5.5	−5.9
Syringic acid	−4.6	−6.3	−5.4	−5.0
Vitexin	−6	−9.3	−8.2	−6.3

Table 3 Interaction residue key protein target with mung bean compound and positive control

Complex docked	Hydrogen bond	Others bond	Shorter distance interaction (Å)
SRC—Dulcinoside	ARG 34, ARG 14, LYS 62	LEU 96[a], TYR 61[b], GLY 95[b], THR 38[c]	1.93
SRC—Dasatinib	THR 38, GLU 37, ARG 14, LYS 62, ILE 73	THR 38[b], CYS 44[e], ARG 14[f], LYS 62[g]	2.31
MAPK8—Dulcinoside	SER 34, LYS 55, GLN 37, ASP 151	ILE 32[b], VAL 40[b], LEU 168[b], ASN 156[d], ARG 69[d], MET 108[e]	2.17
MAPK8—Pyrazolanthrone	–	ILE 32[b], VAL 158[b], LEU 168[b], VAL 40[b], MET 108[e], ALA 53[g], LYS 55[g]	3.66
HSP90AA1—Peonidin-3-glucoside	SER 52, ASN 51, PHE 138, GLY 137, GLY 135	ALA 55[g], MET 98[g], VAL 186[g]	1.77
HSP90AA1—Geldanamycin	ASP 54, SER 53, GLY 137	ASN 51[d]	2.01
HRAS—Chlorogenic Acid	ASP 54, LEU 56, THR 74	LYS 5[a], LEU 6[a], VAL 7[a], SER 39[a], ILE 55[a], GLN 70[a], GLY 75[a], TYR 71[b], MET67[g]	2.16
HRAS—Kobe0065	THR 74	LYS 5[a], VAL 7[a], SER 39[a], ARG 41[a], TYR 71[d], ASP 54[f], LEU 56[g], GLN 70[h]	2.01

[a] Van der walls, [b]Pi-Pi T-Shaped/Pi-Sigma, [c]Unfavorable bump, [d]Carbon Hydrogen Bond, [e]Pi-Sulfur/Sulfur-X interaction, [f]Pi-Cation, [g]Alkyl/Pi-Alkyl Interaction, [h]Halogen

c-Jun N-terminal kinases (JNK), and Extracellular signal-regulated kinase (ERK) proteins play an essential role in cell survival, apoptosis, and cell differentiation [31]. Furthermore, Glutathione Transferase P1 (GSTP1) can be marker of prostate gland carcinogenesis, whereas methylation of GSTP1 is an epigenetics associated with prostate cancer [32].

Furthermore, in cellular component analysis (Fig. 6B), two cellular components involving 56 prostate cancer proteins targeted by the mung bean compounds were

Table 4 Pharmacokinetics Properties of 3 selected mung bean compound and corresponding positive control

	Absorption			Distribution					Metabolism							Excretion
Variable	**Human Intestinal Absorption (% Absorbed)**	**Caco2 permeability**	**Log Kp (skin permeation) (cm/s)**	**P-gp substrate**	**P-gp inhibitor**	**VDss (human) (logL/Kg)**	**BBB Permeation**	**Subcellular localization**	**2D6**	**3A4**	**1A2**	**2C19**	**2C9**	**2D6**	**3A4**	**Total Clearance (log mL/min/kg)**
Dasatinib	83.22	No	−6.73	No	Yes	1.44	Yes	Mitochondria	No	Yes	No	No	No	No	Yes	0.477
Pyrazolanthrone	94.28	No	−5.71	No	No	−0.05	Yes	Mitochondria	Yes	Yes	Yes	No	No	Yes	Yes	0.233
Geldanamycin	61.57	No	−8.31	Yes	Yes	−0.69	No	Mitochondria	No	Yes	No	No	No	No	No	0.949
Kobe0065	82.68	No	−5.15	No	No	−0.4	Yes	Mitochondria	Yes	Yes	Yes	Yes	Yes	No	No	−0.233
Dulcinoside	29.4	No	−10.85	No	No	2.05	No	Mitochondria	No	No	No	No	No	No	No	−0.115
Peonidin-3-Glucoside	50.1	No	−8.8	No	No	0.85	No	Nucleus	No	No	No	No	No	No	No	0.62
Chlorogenic_Acid	36.38	No	−8.76	No	No	0.58	No	Mitochondria	No	No	No	No	No	No	No	0.307

Table 5 Toxicity Properties of 3 selected mung bean compound and corresponding positive control

	Max. tolerated dose (human) (log mg/kg/day)	AMES toxicity	Carcinogens	Hepatotoxicity	Tetrahymena Pyriformis Toxicity pIGC50, ug/L	Acute oral toxicity log(1/(mol/kg))	Oral Rat Acute Toxicity (LD50) (mol/kg)	Oral Rat Chronic Toxicity (log mg/kg_bw/day)
Dasatinib	0.107	No	No	Yes	0.727	1.75	2.68	1.531
Pyrazolanthrone	0.084	Yes	No	No	1.515	1.365	2.38	1.844
Geldanamycin	0.117	No	No	Yes	−0.224	2.155	3.18	1.533
Kobe0065	0.493	Yes	Yes	No	1.221	1.864	3.12	2.317
Dulcinoside	0.472	No	No	No	0.74	1.934	2.52	3.419
Peonidin-3-Glucoside	0.566	No	No	No	0.648	1.507	2.58	4.423
Chlorogenic_Acid	−0.134	No	No	No	1.009	1.835	1.97	2.982

Table 6 Druglikeness of 3 selected mung bean compound

Compound	Molecular weight	MLogP	H Acceptors	H Donors	Molar refractivity	Violation
Peonidin-3-glukoside	463.41	−1.54	11	7	112.76	2
Dulcinoside	578.52	−3.36	14	9	137.83	3
Chlorogenic_Acid	354.31	−1.05	9	6	83.50	1

highlighted, namely ficolin-1-rich granule lumen and endosome lumen. The ficolin-1-rich granule is a cellular component commonly used for prostate cancer metastasis [33, 34]. In addition, endosome involvement can also be one of the biomarkers for prostate cancer diagnosis. Research by Johnson et al. exposed that there is a specific disconnect between the initial cellular endosome (peripheral cells) location and the late cellular endosome (perinuclear cells). This specific disconnect can affect the degradation and signaling processes in prostate cancer cells [35].

Moreover, molecular processes that occur in the body of an organism will affect its biological functions. In this analysis, several biological processes were associated with prostate cancer incidence, namely the glutathione derivative metabolic process and cyclooxygenase pathway. Glutathione and its related parts are essential in tumor initiation, development, and drug resistance. Glutathione is synthesized in the cytosol and plays a vital role in preventing the detrimental effects of reactive oxygen species (ROS) on mitochondria in the electron transport process. Glutathione works do not depend on the amount of antioxidants in cancer cells. In prostate cancer tissue, the circulation of glutathione peroxidase is significantly reduced. Thus, it can change the intracellular environment into a prooxidant state and cause significant changes in gene expression that can lead to malignancy [36, 37]. Meanwhile, the cyclooxygenase pathway, especially cyclooxygenase-2 (COX-2), becomes one that plays a role in the course of prostate cancer. COX-2 is reported to be overexpressed and tends to be elevated in prostate cancer. Studies involving prostate cancer cell line PC-3 and LNCaP suggest upregulation of expression of COX-2 mRNA and increased cell proliferation [38].

Several enrichment pathways in prostate cancer proteins were targeted by mung bean compounds, including nitrogen metabolism, pyrimidine metabolism, and prolactin signaling pathways. All three pathways are associated with the incidence of prostate cancer. Increased nitrogen requirements are considered one of the essential metabolic features of cancer cells. This is due to the ability to maintain proliferative signals in cancer. Cell proliferation must synthesize nucleotides containing essential nitrogen [39]. In prostate cancer, amino acid metabolism plays a vital role in the development of cancer cells. One thing that plays a function is the precursors of nitrogen-containing metabolites, such as purines and pyrimidines, for nucleic acid synthesis [40]. In addition, an increase in the rate of nitrogen metabolism occurs along with an improvement in the metabolic rate of glutamate and aspartate in prostate cancer [41]. Pyrimidines are a component of nucleotides in the process of cell proliferation.

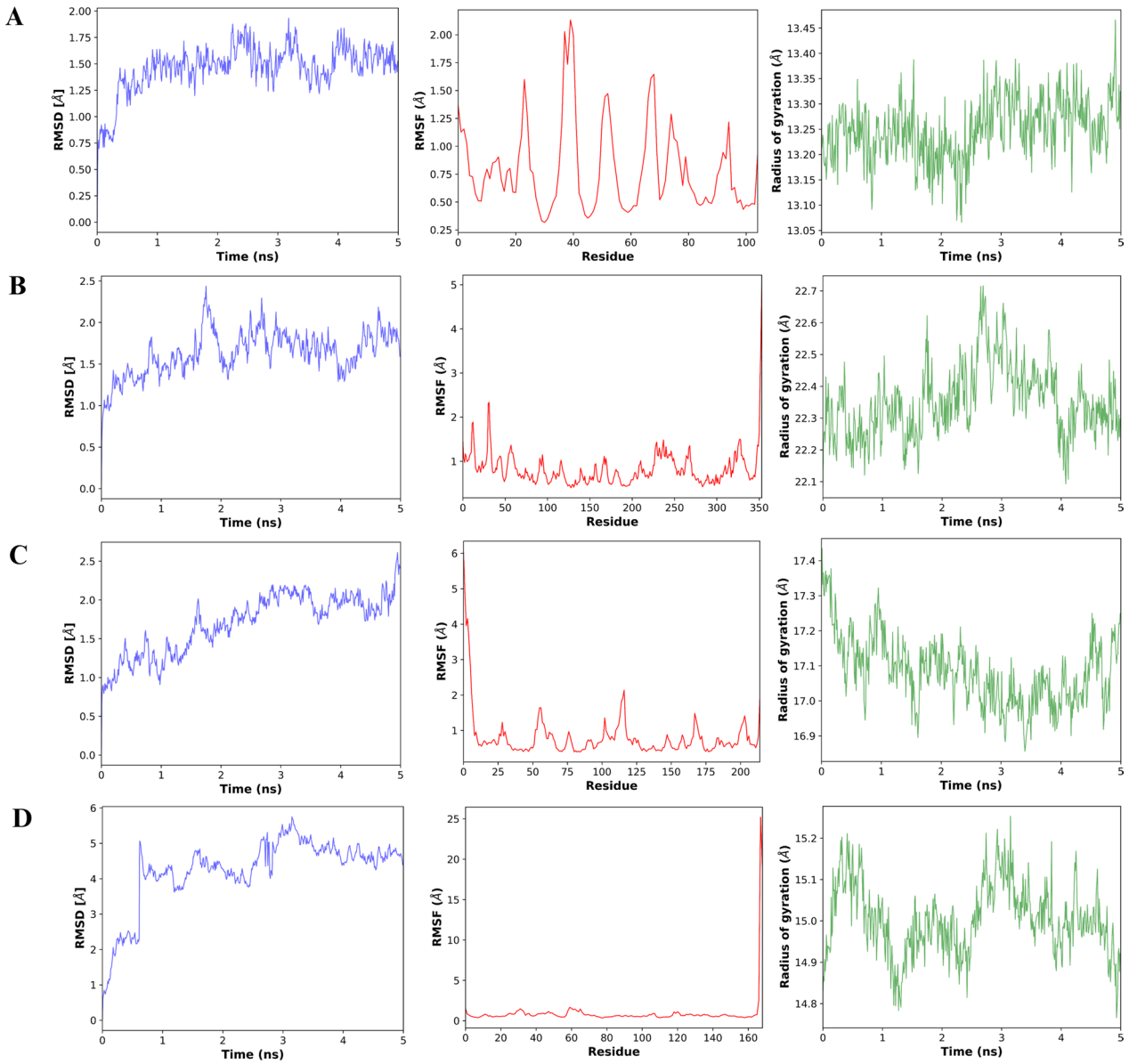


Fig. 9 RMSD, RMSF and Radius of Gyration of selected protein–ligand complexes during molecular dynamic stimulation **A** Dulcinoside-SRC **B** Dulcinoside-MAPK8 **C** Peonidin-3-Glucoside-HSP90AA1 **D** Chlorogenic acid-HRAS

Table 7 Free energy binding of selected protein-mung bean compound complexes during molecular dynamic stimulation

	SRC—Dulcinoside	MAPK8—Dulcinoside	HSP90AA1—Peonidin-3-glucoside	HRAS—Chlorogenic acid
Energy component	Average ± SEM	Average ± SEM	Average ± SEM	Average ± SEM
VDWALLS	− 36.6784 ± 1.60	− 43.6323 ± 1.54	− 40.5494 ± 1.20	− 20.3197 ± 1.80
EEL	− 54.4253 ± 5.46	− 51.3954 ± 2.93	− 43.4504 ± 2.92	− 12.2665 ± 4.57
EGB	60.4523 ± 4.22	66.5217 ± 1.97	55.266 ± 1.88	23.3036 ± 4.70
ESURF	− 5.8672 ± 0.22	− 7.4239 ± 0.20	− 7.0385 ± 0.11	− 3.2707 ± 0.30
ΔG gas	− 91.1037 ± 6.66	− 95.0277 ± 3.47	− 83.9998 ± 2.62	− 32.5862 ± 5.93
ΔG solv	54.5851 ± 4.08	59.0978 ± 1.95	48.2275 ± 1.88	20.0329 ± 4.42
ΔTotal	− 36.5187 ± 2.93	− 35.93 ± 1.67	− 35.7723 ± 1.17	− 12.5533 ± 1.65

The presence of disturbances in the pyrimidine metabolic process is associated with the progression of cancer, including prostate cancer. Research conducted by Kelly et al. revealed pyrimidine metabolism and oxidative phosphorylation were the most dysregulated pathways in the lethal type of prostate tumor ($p < 0.007$) [42]. Furthermore, the hormone Prolactin (PRL) can also play a role in cell proliferation, survival, and tumorigenesis of prostate cancer cells. Suppression of the hormone prolactin can be a consideration in the treatment of prostate cancer [43, 44].

Silico docking and dynamic analysis of 19 polyphenol compounds against four critical proteins, including SRC, MAPK8, HSP90AA1, and HRAS, reveal promising interaction. The results demonstrated that the three best compounds for each protein target, showing the lowest average binding free energy in catalytic site, were dulcinoside, peonidin-3-glucoside, and chlorogenic acid. The smaller binding free energy indicates a better binding affinity of the compound to its protein target. Compounds derived from mung beans had a lower affinity value compared to the control compounds [45]. Therefore, it can be assumed that these compounds have better inhibitory potential than the controls.

The Src protein is one of the proto-oncogenes that play a role in signal transduction during cellular activities, such as cell differentiation, adhesion, and cell migration. This protein plays a role in androgen-dependent and androgen-independent stages of prostate cancer [46]. In vitro, researchers conveyed that the inhibition of this protein can be helpful in the treatment of prostate cancer. The inhibition of Src using Dasatinib has been tested in prostate cancer. The result revealed that Dasatinib could become a suppressor agent for cancer cells and significantly reduce the incidence of lymph gland metastases [47].

The MAPK8/JNK1 protein can act as a proapoptotic agent while also inducing cell proliferation, invasion, and migration [48]. JNK1 ATP-competitive inhibitor, Pyrazolantrhone (SP600125), is less specific than Betamapimod (AS602801). The inhibition of MAPK8/JNK1 protein in prostate cancer cells using JNK inhibitors and enzalutamide can affect cell death, inhibit the proliferation, migration, and invasion of prostate cancer cells, and prevent cell growth. There is opposition to the process of JNK1 inhibition due to the benefits of inhibiting cell proliferation, invasion, and metastasis while inhibiting the function of apoptosis [49].

HSP90AA1 is one of the protein subtypes of the HSP90 family. This protein is located in the cytosol. The HSP90 protein is involved in cellular processes and regulates apoptotic pathways, cell cycles, and signaling. HSP90 protein may promote prostate cancer progression in the Nuclear factor kappa B (NF-kB) pathway. This protein can also regulate the process of prostate cancer proliferation and apoptosis through many pathways such as receptor pathways androgen, human epidermal growth factor receptor 2 (ERBB2), Act, c-RAF, survivin, Epidermal growth factor receptor (EGFR), Insulin-like growth factor 1 (IGFR-1), Signal transducer and activator of transcription 3 (STAT3), ERK, Cyclin-dependent kinase 4 and 6 (CDK-4 and CDK-6) signaling pathways. HSP90 inhibitors as a therapy against cancer can use Geldanamycin, a potent antitumor activity, but this compound has an unstable structure and is hepatotoxic [50].

HRAS is a protein from the RAS family that can contribute to tumorigenesis, invasion, and metastasis of various types of cancer. Inhibiting this protein can be a treatment option to prevent cancer cell proliferation, aggression, and migration [51]. Furthermore, Kobe0065 family compounds can inhibit the interaction of Ras-GTP with many effectors, including RAF, Phosphoinositide 3-kinase (PI3K), Ral guanine nucleotide dissociation stimulator (RalGDS), and Son of Sevenless (SoS). This results in the inhibition of the cellular activity of the HRAS pathway [52]. In addition, the use of Simvastatin in inhibiting Cav1 may decrease the expression of the H-RAS/(PLCε) pathway, which is known to hinder migration Castration Resistant Prostate Cancer (CRPC) [53].

The ADMET profiles of drugs/candidates are essential to drug discovery. Assessment of absorption, distribution, metabolism, excretion, and toxicity is critical to demonstrate. In this study, the absorption component was reviewed by assessing the parameters of intestinal absorption, Caco2 permeability, skin permeation, and P-glycoprotein substrate and inhibitor. The intestinal absorption component can predict the proportion of compounds absorbed through the human small intestine, where a value of < 30% indicates a poor absorption rate. According to Table 4, several compounds had a good absorption rate. Only dulcinoside had a value slightly lower than the threshold, so it can be predicted that this compound will not be absorbed appropriately by the intestine. [54].

Caco2 permeability is one component that can be employed to predict drug absorption when administered orally. It can be done because this model can express cytochrome P450 enzymes, transporters, microvilli, and enterocytes identical to the human small intestine [55]. All test compounds could not penetrate Caco2. Skin permeation is a component that can predict if a drug can penetrate the skin. All test compounds had relatively lower skin permeation values compared to the controls, so it can be said that they are poorly permeable to the skin [56]. Furthermore, they also showed no potential

substrate or inhibitor for P-glycoprotein (P-gp). Hence, P-gp could not actively transport them, and the efflux activity of P-gp was reduced [57, 58].

In this study, distribution parameters in the test components were Volume Distribution steady state (VDss) and Blood blood–brain barrier (BBB) permeation. VDss is a component that can predict the total dose of the drug distributed in tissues. It is considered low if the VDss log value is < -0.15, while high if the value is > 0.45. Based on Table 4, all test compounds had high VDss log values, so these compounds are predicted to have good network distribution capabilities [54, 59]. Further, BBB permeation refers to the ability of a compound to be permeable to the blood–brain barrier. The results revealed that all test compounds are predicted to have poor permeability to BBB [60]. Therefore, these compounds are not suitable when used in cases of prostate cancer that metastasizes to the brain. However, these compounds need to be retested in vitro or in vivo to assess the permeability quality of BBB compounds. In addition, a substrate such as BBB permeabilizer kinin analogs can be added to increase the permeability of the BBB so that the compound can pass through the BBB and affect its biological target [61].

Furthermore, metabolic predictions in this test included the ability to inhibit CYP2D6, CYP3A4, CYP1A2, CYP2C19, and CYP2C9 and substrates of CYP2D6 and CYP3A4, which are the amino acid residues. All test enzymes are part of the cytochrome P450 family, which is very important clinically and plays a role in drug metabolism [54, 59, 62–64]. Several anticancer drugs often must be metabolized by cytochrome P450 enzymes to become active or be excreted from the body, such as tamoxifen, an antiestrogen drug for treating breast cancer [65].

All test compounds could not inhibit all test enzymes and were not substrates of CYP2D6 and CYP3A4. Hence, it can be concluded that the compounds will not impede the work and will not be metabolized by cytochrome P450. Besides metabolism, components excrete compounds in the body by assessing the approximate total cleansing log (CLtot). The total clearance value can be applied as a reference in determining the dose of the drug and understanding the mechanism by which the drug is removed from the body [66, 67]. The last parameter tested was toxicity, while the components evaluated were max tolerated dose, AMES toxicity, Carcinogens, hepatoxicity, Tetrahymena Pyriformis toxicity, Acute oral toxicity, oral rat acute toxicity (LD50), and oral rat chronic toxicity (LOAEL). Tetrahymena Pyriformis toxicity value demonstrates the total dose of the molecule for the inhibition of *T. Pyriformis* by 50% of growth. The LD50 value refers to the dose of a substance killing 50% of the tested sample. Meanwhile, the LOAEL value denotes the minimum amount of a sense that can have side effects when consumed in the long term. LD50 and LOAEL values can be employed as a reference to determine safe and effective drug doses and assess potential harm to the organism [68, 69].

AMES toxicity is commonly used to understand better and predict DNA mutation affected by a given chemical [70]. At the same time, carcinogens are conducted to assess the chemical ability to induce carcinogenesis [70], and hepatotoxicity is tested to predict the chemical ability to be toxic to the liver [54]. In this study, it is found that all test compounds potentially did not have toxicity to the AMES model, did not possess carcinogens, and were toxic to the liver. The analysis of the drug-likeness aspect using the Lipinski of 5 rules assesses molecular weight parameters (< 500), hydrogen donors (< 5), hydrogen acceptors (< 10), LogP (< 5) or MLogP ($< 4{,}15$), and Molar Refractivity (40–130) [71]. The molecular weight parameter can indicate the ability of a compound to be absorbed through the wall of the small intestine. Hydrogen donor and hydrogen acceptor refer to the ability of compounds to interact and be soluble in water. Furthermore, the MLog P parameter is an indicator of lipophilicity. The higher the MLog P value, the more lipophilic a compound is. Last, molar refractivity refers to the ability of a compound to interact appropriately with its biological targets [72, 73].

An orally active compound should not have more than one violation. If a compound violates more than one parameter, the gastrointestinal tract is difficult to absorb, and its bioavailability is low. Despite this, many drugs violate Lipinski's rules but are still orally active. Lipinski's rule predicts a compound with the ability to diffuse passively. This rule is less relevant if a compound is a substrate transporter so that it can actively diffuse [72, 73]. Therefore, further pharmacokinetic properties testing should be performed to assess the ADMET component of the tested compound.

Based on this analysis, test compounds with > 1 violation of Lipinski's rule should not be taken orally. Still, a method of delivery is created so that the drug reaches its biological target, such as intravenously, intramuscularly, buccal, or anally [74]. In addition, it can use a nanoparticle as a delivery so that complex compounds can be easily absorbed and enter the cell to have biological effects on its target. Furthermore, these compounds can still be administered orally with the help of some absorption-enhancing components such as chitosan, surfactants, bile salts, nano-carrier, nano-emulsion, and dendrimers [75].

6 Conclusion

In summary, it can be concluded that the potential proteins related to prostate cancer from network pharmacology analysis were SRC, MAPK8, HSP90AA1, and HRAS. KEGG analysis revealed 206 mechanism pathways potentially associated with prostate cancer pathogenesis, including nitrogen metabolism, pyrimidine metabolism, and prolactin signaling pathway. Molecular docking results indicated that the test compounds had binding free energy values better than their controls. The compact and stable interaction assumed that the three best compounds (dulcinoside, peonidin-3-glucoside, and chlorogenic acid) had a better effect than drug control. Furthermore, the analysis revealed that the compounds are predicted to have a good pharmacokinetics and toxicology profile. However, studies should be conducted to verify the effectivity of mung bean compounds in prostate cancer, such as in vitro and in vivo studies.

Abbreviations

CRPC	Castration-Resistant Prostate Cancer
CYP	Cytochrome
GO	Gene ontology
HRAS	Harvey Rat sarcoma virus
HSP90AA1	Heat shock protein 90 kDa alpha (cytosolic), member A1
KEGG	Kyoto Encyclopedia of Genes and Genomes
LD50	Lethal Dose 50
MAPK	Mitogen-Activated Protein Kinase
OMIM	Online Mendelian Inheritance in Man
P3G	Peonidin-3-glucoside
PPI	Protein-protein interaction
PI3K	Phosphoinositide-3-Kinase
Raf	Rapidly accelerated fibrosarcoma
Ras	Rat sarcoma
SMILES	Simplified molecular-input line-entry specification
Src	Sarcoma

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Declarations

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Consent for publication

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Competing interests

The authors declare no conflict of interest.

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References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F (2021) Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 71(3):209–249. https://doi.org/10.3322/caac.21660
2. Putri RGP, Ysrafil Y, Awisarita W (2022) Cancer incidence in volcanic areas: a systematic review. APJCP 23(6):1817–1826. https://doi.org/10.31557/apjcp.2022.23.6.1817
3. Michael C, Barnett F, Gray M (2016) The experiences of prostate cancer survivors: changes to physical function and its impact on quality of life. Int J Ther Rehabil 23(7):323–330. https://doi.org/10.12968/ijtr.2016.23.7.323
4. Popiołek A, Brzoszczyk B, Jarzemski P, Piskunowicz M, Jarzemski M, Borkowska A, Bieliński M (2022) Quality of life of prostate cancer patients undergoing prostatectomy and affective temperament. Cancer Manag Res 14:1743–1755. https://doi.org/10.2147/cmar.S358054
5. Fall K, Fang F, Mucci LA, Ye W, Andrén O, Johansson JE, Andersson SO, Sparén P, Klein G, Stampfer M, Adami HO, Valdimarsdóttir U (2009) Immediate risk for cardiovascular events and suicide following a prostate cancer diagnosis: prospective cohort study. PLoS Med 6(12):e1000197. https://doi.org/10.1371/journal.pmed.1000197
6. Noce A, Di Lauro M, Di Daniele F, Pietroboni Zaitseva A, Marrone G, Borboni P, Di Daniele N (2021) Natural bioactive compounds useful in clinical management of metabolic syndrome. Nutrients. https://doi.org/10.3390/nu13020630
7. Panche AN, Diwan AD, Chandra SR (2016) Flavonoids: an overview. J Nutr Sci 5:e47. https://doi.org/10.1017/jns.2016.41
8. Ganesan K, Xu B (2018) A critical review on phytochemical profile and health promoting effects of mung bean (Vigna radiata). Food Sci Hum Wellness 7(1):11–33. https://doi.org/10.1016/j.fshw.2017.11.002
9. Hou D, Yousaf L, Xue Y, Hu J, Wu J, Hu X, Feng N, Shen Q (2019) Mung bean (Vigna radiata L): bioactive polyphenols, polysaccharides, peptides, and health benefits. Nutrients. https://doi.org/10.3390/nu11061238
10. Lin BW, Gong CC, Song HF, Cui YY (2017) Effects of anthocyanins on the prevention and treatment of cancer. Br J Pharmaco 174(11):1226–1243. https://doi.org/10.1111/bph.13627
11. Musial C, Kuban-Jankowska A, Gorska-Ponikowska M (2020) Beneficial properties of green tea catechins. Int J Mol Sci. https://doi.org/10.3390/ijms21051744
12. Ysrafil Y, Sapiun Z, Slamet NS, Mohamad F, Hartati H, Damiti SA, Alexandra FD, Rahman S, Masyeni S, Harapan H, Mamada SS, Bin Emran T, Nainu F (2023) Anti-inflammatory activities of flavonoid derivates. Admet DMPK 11(3):331–359. https://doi.org/10.5599/admet.1918
13. Qattan MY, Khan MI, Alharbi SH, Verma AK, Al-Saeed FA, Abduallah AM, Al Areefy AA (2022) Therapeutic importance of kaempferol in the treatment of cancer through the modulation of cell signalling pathways. Molecules (Basel, Switzerland). https://doi.org/10.3390/molecules27248864
14. Vafadar A, Shabaninejad Z, Movahedpour A, Fallahi F, Taghavipour M, Ghasemi Y, Akbari M, Shafiee A, Hajighadimi S, Moradizarmehri S, Razi E, Savardashtaki A, Mirzaei H (2020) Quercetin and cancer: new insights into its therapeutic effects on ovarian cancer cells. Cell Biosci 10:32. https://doi.org/10.1186/s13578-020-00397-0

15. Ganesan K, Xu B (2017) Molecular targets of vitexin and isovitexin in cancer therapy: a critical review. Ann N Y Acad Sci 1401(1):102–113. https://doi.org/10.1111/nyas.13446
16. He M, Min JW, Kong WL, He XH, Li JX, Peng BW (2016) A review on the pharmacological effects of vitexin and isovitexin. Fitoterapia 115:74–85. https://doi.org/10.1016/j.fitote.2016.09.011
17. Alam MA, Subhan N, Hossain H, Hossain M, Reza HM, Rahman MM, Ullah MO (2016) Hydroxycinnamic acid derivatives: a potential class of natural compounds for the management of lipid metabolism and obesity. Nutr Metab 13:27. https://doi.org/10.1186/s12986-016-0080-3
18. Nwafor EO, Lu P, Zhang Y, Liu R, Peng H, Xing B, Liu Y, Li Z, Zhang K, Zhang Y, Liu Z (2022) Chlorogenic acid: potential source of natural drugs for the therapeutics of fibrosis and cancer. Transl Oncol 15(1):101294. https://doi.org/10.1016/j.tranon.2021.101294
19. Pei K, Ou J, Huang J, Ou S (2016) p-Coumaric acid and its conjugates: dietary sources, pharmacokinetic properties and biological activities. J Sci Food Agric 96(9):2952–2962. https://doi.org/10.1002/jsfa.7578
20. Subramanian AP, Jaganathan SK, Mandal M, Supriyanto E, Muhamad II (2016) Gallic acid induced apoptotic events in HCT-15 colon cancer cells. WJG 22(15):3952–3961. https://doi.org/10.3748/wjg.v22.i15.3952
21. Hopkins AL (2007) Network pharmacology. Nat Biotechnol 25(10):1110–1111. https://doi.org/10.1038/nbt1007-1110
22. Noor F, Tahir Ul Qamar M, Ashfaq UA, Albutti A, Alwashmi ASS, Aljasir MA (2022) Network pharmacology approach for medicinal plants: review and assessment. Pharmaceuticals (Basel, Switzerland). https://doi.org/10.3390/ph15050572
23. Morris GM, Lim-Wilby M (2008) Molecular docking. Methods Mol Biol (Clifton, NJ) 443:365–382. https://doi.org/10.1007/978-1-59745-177-2_19
24. Pinzi L, Rastelli G (2019) Molecular docking: shifting paradigms in drug discovery. Int J Mol Sci. https://doi.org/10.3390/ijms20184331
25. Tang D, Dong Y, Ren H, Li L, He C (2014) A review of phytochemistry, metabolite changes, and medicinal uses of the common food mung bean and its sprouts (Vigna radiata). Chem Cent J 8(1):4. https://doi.org/10.1186/1752-153x-8-4
26. Alotaibi NM, Alotaibi MO, Alshammari N, Adnan M, Patel M (2023) Network pharmacology combined with molecular docking, molecular dynamics, and in vitro experimental validation reveals the therapeutic potential of Thymus vulgaris L. essential oil (thyme oil) against human breast cancer. ACS Omega 8(50):48344–48359. https://doi.org/10.1021/acsomega.3c07782
27. Long S, Ji S, Xue P, Xie H, Ma Y, Zhu S (2022) Network pharmacology and molecular docking analysis reveal insights into the molecular mechanism of Shiliao decoction in the treatment of cancer-associated malnutrition. Front Nutr 9:985991. https://doi.org/10.3389/fnut.2022.985991
28. Arwansyah A, Lewa AF, Muliani M, Warnasih S, Mustopa AZ, Arif AR (2023) Molecular recognition of moringa oleifera active compounds for stunted growth prevention using network pharmacology and molecular modeling approach. ACS Omega 8(46):44121–44138. https://doi.org/10.1021/acsomega.3c06379
29. Shahzadi Z, Yousaf Z, Anjum I, Bilal M, Yasin H, Aftab A, Booker A, Ullah R, Bari A (2024) Network pharmacology and molecular docking: combined computational approaches to explore the antihypertensive potential of Fabaceae species. BIOB 11(1):53. https://doi.org/10.1186/s40643-024-00764-6
30. Fontana F, Raimondi M, Marzagalli M, Di Domizio A, Limonta P (2020) Natural compounds in prostate cancer prevention and treatment: mechanisms of action and molecular targets. Cells. https://doi.org/10.3390/cells9020460
31. Rodríguez-Berriguete G, Fraile B, Martínez-Onsurbe P, Olmedilla G, Paniagua R, Royuela M (2012) MAP kinases and prostate cancer. J Signal Transduct 2012:169170. https://doi.org/10.1155/2012/169170
32. Martignano F, Gurioli G, Salvi S, Calistri D, Costantini M, Gunelli R, De Giorgi U, Foca F, Casadio V (2016) GSTP1 methylation and protein expression in prostate cancer: diagnostic implications. Dis Markers 2016:4358292. https://doi.org/10.1155/2016/4358292
33. Li C, Zhu J, Du H, Liang C (2022) Identification of novel pyroptosis-related gene signatures to predict prostate cancer recurrence. Front Oncol 12:814912. https://doi.org/10.3389/fonc.2022.814912
34. Samaržija I (2021) Site-specific and common prostate cancer metastasis genes as suggested by meta-analysis of gene expression data. Life (Basel, Switzerland). https://doi.org/10.3390/life11070636
35. Johnson IR, Parkinson-Lawrence EJ, Shandala T, Weigert R, Butler LM, Brooks DA (2014) Altered endosome biogenesis in prostate cancer has biomarker potential. MCR 12(12):1851–1862. https://doi.org/10.1158/1541-7786.Mcr-14-0074
36. Bansal A, Simon MC (2018) Glutathione metabolism in cancer progression and treatment resistance. JCB 217(7):2291–2298. https://doi.org/10.1083/jcb.201804161
37. Tan BL, Norhaizan ME (2021) Oxidative stress, diet and prostate cancer. World J Mens Health 39(2):195–207. https://doi.org/10.5534/wjmh.200014
38. Aparicio Gallego G, Díaz Prado S, Jiménez Fonseca P, García Campelo R, Cassinello Espinosa J, Antón Aparicio LM (2007) Cyclooxygenase-2 (COX-2): a molecular target in prostate cancer. Clin Transl Oncol 9(11):694–702. https://doi.org/10.1007/s12094-007-0126-0
39. Pavlova NN, Thompson CB (2016) The emerging hallmarks of cancer metabolism. Cell Metab 23(1):27–47. https://doi.org/10.1016/j.cmet.2015.12.006
40. Ahmad F, Cherukuri MK, Choyke PL (2021) Metabolic reprogramming in prostate cancer. Br J Cancer 125(9):1185–1196. https://doi.org/10.1038/s41416-021-01435-5
41. Taylor BS, Pal M, Yu J, Laxman B, Kalyana-Sundaram S, Zhao R, Menon A, Wei JT, Nesvizhskii AI, Ghosh D, Omenn GS, Lubman DM, Chinnaiyan AM, Sreekumar A (2008) Humoral response profiling reveals pathways to prostate cancer progression. MCP 7(3):600–611. https://doi.org/10.1074/mcp.M700263-MCP200
42. Kelly RS, Sinnott JA, Rider JR, Ebot EM, Gerke T, Bowden M, Pettersson A, Loda M, Sesso HD, Kantoff PW, Martin NE, Giovannucci EL, Tyekucheva S, Heiden MV, Mucci LA (2016) The role of tumor metabolism as a driver of prostate cancer progression and lethal disease: results from a nested case-control study. Cancer metab 4:22. https://doi.org/10.1186/s40170-016-0161-9
43. Costello LC (2019) The suppression of prolactin is required for the treatment of advanced prostate cancer. Oncogen. https://doi.org/10.35702/onc.10013
44. Sackmann-Sala L, Goffin V (2015) Prolactin-induced prostate tumorigenesis. Adv Exp Med Biol 846:221–242. https://doi.org/10.1007/978-3-319-12114-7_10
45. Suhandi C, Fadhilah E, Silvia N, Atusholihah A, Prayoga RR, Megantara S, Muchtaridi M (2021) Molecular docking study of mangosteen (Garcinia mangostana L.) xanthone-derived isolates as anti androgen. IJCC 12(1):11–20. https://doi.org/10.14499/indonesianjcanchemoprev12iss1pp11-20
46. Fizazi K (2007) The role of Src in prostate cancer. Ann Oncol 18(11):1765–1773. https://doi.org/10.1093/annonc/mdm086
47. Araujo J, Logothetis C (2010) Dasatinib: a potent SRC inhibitor in clinical development for the treatment of solid tumors. Cancer Treat Rev 36(6):492–500. https://doi.org/10.1016/j.ctrv.2010.02.015
48. Xu R, Hu J (2020) The role of JNK in prostate cancer progression and therapeutic strategies. Biomed Pharmacother 121:109679. https://doi.org/10.1016/j.biopha.2019.109679
49. Li Z, Sun C, Tao S, Osunkoya AO, Arnold RS, Petros JA, Zu X, Moreno CS (2020) The JNK inhibitor AS602801 synergizes with enzalutamide to kill prostate cancer cells in vitro and in vivo and inhibit androgen receptor expression. Transl Oncol 13(4):100751. https://doi.org/10.1016/j.tranon.2020.100751
50. Fu X, Liu J, Yan X, DiSanto ME, Zhang X (2022) Heat shock protein 70 and 90 family in prostate cancer. Life (Basel, Switzerland). https://doi.org/10.3390/life12101489
51. Sugita S, Enokida H, Yoshino H, Miyamoto K, Yonemori M, Sakaguchi T, Osako Y, Nakagawa M (2018) HRAS as a potential therapeutic target of salirasib RAS inhibitor in bladder cancer. Int J Oncol 53(2):725–736. https://doi.org/10.3892/ijo.2018.4435
52. Shima F, Yoshikawa Y, Ye M, Araki M, Matsumoto S, Liao J, Hu L, Sugimoto T, Ijiri Y, Takeda A, Nishiyama Y, Sato C, Muraoka S, Tamura A, Osoda T, Tsuda K, Miyakawa T, Fukunishi H, Shimada J, Kumasaka T, Yamamoto M, Kataoka T (2013) In silico discovery of small-molecule Ras inhibitors that display antitumor activity by blocking the Ras-effector interaction. Proc Natl Acad Sci USA 110(20):8182–8187. https://doi.org/10.1073/pnas.1217730110

53. Bian Q, Li B, Zhang L, Sun Y, Zhao Z, Ding Y, Yu H (2023) Molecular pathogenesis, mechanism and therapy of Cav1 in prostate cancer. Discov Oncol 14(1):196. https://doi.org/10.1007/s12672-023-00813-0
54. Pires DE, Blundell TL, Ascher DB (2015) pkCSM: predicting small-molecule pharmacokinetic and toxicity properties using graph-based signatures. J Med Chem 58(9):4066–4072. https://doi.org/10.1021/acs.jmedchem.5b00104
55. Awortwe C, Fasinu PS, Rosenkranz B (2014) Application of Caco-2 cell line in herb-drug interaction studies: current approaches and challenges. JPPS 17(1):1–19. https://doi.org/10.18433/j30k63
56. Daina A, Michielin O, Zoete V (2017) SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. Sci Rep 7:42717. https://doi.org/10.1038/srep42717
57. Lin JH, Yamazaki M (2003) Role of P-glycoprotein in pharmacokinetics: clinical implications. Clin Pharmacokinet 42(1):59–98. https://doi.org/10.2165/00003088-200342010-00003
58. Seelig A (2020) P-glycoprotein: one mechanism, many tasks and the consequences for pharmacotherapy of cancers. Front oncol 10:576559. https://doi.org/10.3389/fonc.2020.576559
59. Yeni Y, Rizky AR (2022) The prediction of pharmacokinetic properties of compounds in Hemigraphis alternate (Burm. F.) t. ander leaves using pkCSM. Indones J Chem 22(4):1081–1089. https://doi.org/10.22146/ijc.73117
60. Dirar AI, Waddad AY, Mohamed MA, Mohamed MS, Osman WJ, Mohammed MS, Elbadawi MA, Hamdoun S (2016) In silico pharmacokinetics and molecular docking of three leads isolated from Tarconanthus camphoratus L. Int J Pharm Pharm Sci 8(5):71–77
61. Sikpa D, Whittingstall L, Savard M, Lebel R, Côté J, McManus S, Chemtob S, Fortin D, Lepage M, Gobeil F (2020) Pharmacological modulation of blood-brain barrier permeability by kinin analogs in normal and pathologic conditions. Pharmaceuticals (Basel, Switzerland). https://doi.org/10.3390/ph13100279
62. Hakkola J, Hukkanen J, Turpeinen M, Pelkonen O (2020) Inhibition and induction of CYP enzymes in humans: an update. Arch Toxicol 94(11):3671–3722. https://doi.org/10.1007/s00204-020-02936-7
63. Jing J, Chen Y, Musib L, Jin JY, Cheung KWK, Yoshida K, Sane R (2022) Assessment of cytochrome P450 3A4-mediated drug-drug interactions for ipatasertib using a fit-for-purpose physiologically based pharmacokinetic model. CCAP 89(5):707–720. https://doi.org/10.1007/s00280-022-04434-2
64. Molden E, Jukić MM (2021) CYP2D6 reduced function variants and genotype/phenotype translations of CYP2D6 intermediate metabolizers: implications for personalized drug dosing in psychiatry. Front pharmacol 12:650750. https://doi.org/10.3389/fphar.2021.650750
65. Stipp MC, Acco A (2021) Involvement of cytochrome P450 enzymes in inflammation and cancer: a review. CCAP 87(3):295–309. https://doi.org/10.1007/s00280-020-04181-2
66. Morita-Ogawa T, Sugita H, Minami H, Yamaguchi T, Hanada K (2020) Population pharmacokinetics and renal toxicity of cisplatin in cancer patients with renal dysfunction. CCAP 86(4):559–566. https://doi.org/10.1007/s00280-020-04147-4
67. Talevi A (2022) The ADME encyclopedia: a comprehensive guide on biopharmacy and pharmacokinetics. Springer, Berlin
68. Gadaleta D, Vuković K, Toma C, Lavado GJ, Karmaus AL, Mansouri K, Kleinstreuer NC, Benfenati E, Roncaglioni A (2019) SAR and QSAR modeling of a large collection of LD(50) rat acute oral toxicity data. J Cheminf 11(1):58. https://doi.org/10.1186/s13321-019-0383-2
69. Li X, Zhang Y, Chen H, Li H, Zhao Y (2017) In silico prediction of chronic toxicity with chemical category approaches. RSC adv 7(66):41330–41338
70. Mortelmans K, Zeiger E (2000) The Ames Salmonella/microsome mutagenicity assay. Mutat Res 455(1–2):29–60. https://doi.org/10.1016/s0027-5107(00)00064-6
71. Daina A, Michielin O, Zoete V (2019) SwissTargetPrediction: updated data and new features for efficient prediction of protein targets of small molecules. NAR 47(W1):W357-w364. https://doi.org/10.1093/nar/gkz382
72. Pollastri MP (2010) Overview on the rule of five. Curr Protoc Pharmacol 9:12. https://doi.org/10.1002/0471141755.ph0912s49
73. Agoni C, Olotu FA, Ramharack P, Soliman ME (2020) Druggability and drug-likeness concepts in drug design: are biomodelling and predictive tools having their say? J Mol Model 26(6):120. https://doi.org/10.1007/s00894-020-04385-6
74. Kim J, De Jesus O (2023) Medication routes of administration. In: StatPearls. StatPearls Publishing Copyright © 2023, StatPearls Publishing LLC., Treasure Island (FL) companies. Disclosure: Orlando De Jesus declares no relevant financial relationships with ineligible companies
75. Azman M, Sabri AH, Anjani QK, Mustaffa MF, Hamid KA (2022) Intestinal absorption study: challenges and absorption enhancement strategies in improving oral drug delivery. Pharmaceuticals (Basel, Switzerland). https://doi.org/10.3390/ph15080975

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