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Targeting Prostate Cancer with Rambutan Peel-Derived Compounds via Network Pharmacology

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Abstract

Prostate cancer is a prevalent malignancy in men, originating in the prostate gland and often driven by genetic alterations and hormonal dysregulation. Rambutan (*Nephelium lappaceum* L.) peel, a byproduct of fruit consumption, has demonstrated potential anticancer activity. This study employed a network pharmacology-based in silico approach to evaluate the therapeutic potential of rambutan peel extract in prostate cancer treatment. Database searches identified bioactive compounds and predicted their biological activities using PASS Online. To evaluate safety and drug-like properties, pharmacokinetic and toxicity profiles were assessed using ADMETLab 3.0 and Protox 3.0. Potential target proteins were identified via SwissTargetPrediction and GeneCards, while protein-protein interaction networks were constructed using STRING. The pharmacological networks were visualized using Cytoscape to elucidate molecular mechanisms of action. The analysis identified 28 bioactive compounds in rambutan peel extract, with 11 demonstrating activity against prostate cancer (Pa > 0.5). Based on Lipinski's Rule of Five (Ro5), these compounds were deemed safe and categorized within toxicity classes V and VI. Rambutan peel extract was found to target 501 proteins associated with prostate cancer, including key pathways involved in resistance to EGFR tyrosine kinase inhibitors. Network pharmacology analysis highlighted several key target genes, including SRC, GNAI1, PIK3CA, PIK3CD, MAPK1, MAPK3, AKT1, GNAI3, PRKCA, and HSP90AA1. Among these, SRC exhibited the highest centrality score, underscoring its pivotal role in disrupting tumorigenic and metastatic signaling pathways, suppressing cancer cell proliferation, and enhancing therapeutic responses. These findings suggest that rambutan peel extract holds promise as a natural therapeutic agent for prostate cancer, warranting further experimental and clinical validation.

1. Introduction

Prostate cancer is one of the most common malignancies affecting men, with adenocarcinoma being the most common histologic subtype. Based on Global Cancer Observatory (GLOBOCAN) 2022 data, prostate cancer is listed as the fourth highest incidence of cancer globally, with 1,467,854 new cases and 397,430 deaths worldwide [1–3]. The incidence of prostate cancer begins to increase after men turn 55 years old, peaking at 70-74 years of age in the elderly [4]. Among the continents, Asia records the lowest prostate cancer mortality rates, particularly in East Asia and Central-South Asia [5]. Prostate cancer accounts for 7% of total male cancer cases in Indonesia. As many as 70% of new cases are diagnosed at an advanced stage, indicating a delay in detection and treatment [2, 6].

Various treatment modalities for prostate cancer have been developed, with conventional therapies such as surgery, radiation therapy, chemotherapy, and hormone therapy being the primary options [7]. However, these interventions are often associated with considerable side effects that can negatively impact patients' quality of life [8–10]. Radical prostatectomy carries the risk of urinary incontinence and erectile dysfunction, while external radiotherapy is more at risk of causing fecal incontinence [11, 12]. Brachytherapy can result in pain, infection, and possible resistance to therapy [11, 13]. Hormonal therapy often faces treatment resistance and can have significant side effects, including erectile dysfunction and increased risk of cardiovascular disease [14–17]. Consequently, there is a growing focus on alternative therapeutic approaches. One promising avenue is the exploration of natural compounds, which are increasingly sought after for their poly-pharmacological properties and perceived safety profile, offering minimal side effects [18, 19].

The development of natural-based anticancer agents necessitates the evaluation of active compounds with cytotoxic and antimitotic properties and the capacity to inhibit cancer cell proliferation, which are commonly found in plant-derived secondary metabolites [20, 21]. One promising plant is rambutan (*Nephelium lappaceum* L.), which is native to Southeast Asia, including Indonesia. The peel of rambutan is rich in secondary metabolites, including flavonoids, tannins, saponins, and anthocyanins, which have demonstrated anti-inflammatory, antiviral, cardioprotective, immunomodulatory, and anticancer properties [22–24]. These bioactive compounds contribute to various stages of cancer suppression, such as inhibiting tumorigenesis by inducing cell cycle arrest, preventing cancer cell differentiation, and promoting apoptosis [25, 26]. Rambutan (*Nephelium lappaceum* L.) peel was chosen as a source of bioactive compounds in prostate cancer research due to its high phenolic content, especially ellagitannins such as geraniin and corilagin [27–29]. These compounds have been shown to have antiproliferative activity through the mechanism of inhibition of cancer cell signaling pathways, including the inhibition of transcription factor NF-κB and PI3K/Akt pathways, which play an important role in prostate cancer development [22, 28].

In addition, ellagitannin's metabolite, urolithin, which is formed in the body after ingestion of this compound, has been reported to suppress androgen receptor (AR) expression and inhibit the proliferation of androgen-dependent prostate cancer cells [29]. Previous in vitro studies have also shown that rambutan peel extract can induce apoptosis and inhibit the cancer cell cycle in various cell lines, indicating its therapeutic potential against prostate cancer [22].

Methanolic and butanolic extracts of rambutan fruit peels have been evaluated on various cancer cell lines and normal Madin-Darby Canine Kidney (MDCK) cells, demonstrating significant antiproliferative activity while exhibiting low cytotoxicity toward MDCK cells. These findings suggest minimal potential side effects on normal cells [29]. Methanolic and butanolic extracts from rambutan peel have been evaluated on various cancer cell lines, including colorectal cancer (Caco-2) and breast cancer (MDA-MB-231), to assess their antiproliferative potential [27, 29, 30]. In those studies, the extract was evaluated using the MTT (3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) method to measure cell viability [27]. Results showed that the extract could significantly inhibit cancer cell growth with concentration-dependent inhibition [27]. This study continues previous studies by exploring the potential of rambutan peel as an anti-prostate cancer agent. Different from previous studies that focused on colorectal and breast cancer, this study adopted a more comprehensive approach with a network pharmacology analysis method on prostate cancer cells [27, 29].

Despite this promising potential for pharmaceutical development and therapeutic applications, the utilization of rambutan peel remains suboptimal and underexplored; to date, no study has systematically mapped the molecular interactions of its active compounds with specific protein targets in prostate cancer [12, 13, 16]. Most previous studies focused more on evaluating the antiproliferative effects against other cancer cell lines, such as Caco-2, without in-depth analysis of the molecular mechanisms underlying their biological activities [31, 32]. Therefore, a network pharmacology approach was used in this study to comprehensively identify potential molecular targets

through analyzing the interaction of bioactive compounds with prostate cancer-related biological pathways [33]. This method has advantages over conventional approaches, such as in vitro assays, as it allows simultaneous mapping of various molecular pathways that play a role in cancer development. For example, geraniin interacts with various biological targets, including antioxidant, immunomodulatory, and cytoprotective mechanisms that contribute to its broader anticancer effects [28, 33].

2. Materials and Methods

2.1. Rambutan Peel-Derived Compounds Profiling

Information on the secondary metabolites in rambutan fruit peels was obtained from the PubMed database. At the same time, additional chemical compound data were retrieved from PubChem, a database managed by the National Center for Biotechnology Information (NCBI) under the U.S. National Library of Medicine. A systematic literature search was conducted in PubMed using the keywords "prostate cancer," "rambutan peel," "bioactive compounds," and "network pharmacology," along with relevant synonyms based on Medical Subject Headings (MeSH) for comprehensive coverage. Studies were included if they (1) were published in peer-reviewed journals between 2014 and 2024, (2) investigated the bioactivity of rambutan peel compounds in cancer-related molecular mechanisms, and (3) were available in full-text English. Exclusion criteria encompassed studies available only as abstracts, literature reviews lacking primary data, and those unrelated to the molecular or pharmacological properties of rambutan peel compounds in cancer research.

2.2. Analytical Methods

Data analysis utilized online resources, including Dr. Duke's Phytochemical database, PubMed, PubChem, WAY2DRUG PASS, ADMETLab, Protox III, SEA, Swiss Target Prediction, STRING, and Cytoscape. Rambutan peel compounds were obtained from Dr. Duke's database, profiled through PubChem for SMILES, and evaluated for bioactivity and drug-likeness using WAY2DRUG PASS and ADMETLab.

This study employed pharmacological prediction tools, including WAY2DRUG PASS, ADMETLab, and Protox III, to assess the pharmacological activity, pharmacokinetics, and toxicity of bioactive compounds in rambutan peel. In WAY2DRUG PASS, the probability of activity (Pa) and inactivity (Pi) were analyzed, with Pa > 0.7 indicating a strong correlation with experimental activity [20, 34, 35]. ADMETLab evaluated key pharmacokinetic parameters, such as human intestinal absorption (HIA), blood-brain barrier (BBB) permeability, and CYP450-mediated metabolism, which are crucial for drug development [36]. Protox III predicted acute toxicity based on LD50 values, providing insights into the compound's safety profile [37]. The selection of these parameters follows established pharmacology and toxicology standards, ensuring predictive reliability and reinforcing the study's relevance in developing natural compound-based therapeutic agents [33, 36, 37].

Protein interactions with rambutan peel compounds were assessed through Swiss Target Prediction and SEA, and cancer-related proteins were sourced from GeneCards. The intersections of target proteins were analyzed using the Venn Diagram tool. KEGG pathway analysis via ShinyGO identified relevant biological pathways associated with prostate cancer, and a protein interaction network was constructed using STRING-DB. Finally, central prostate cancer-related proteins were identified through Cytoscape, using CytoHubba to analyze degree centrality and identify the most highly connected proteins

2.3. Methodology for Analyzing Bioactive Compounds of Rambutan Fruit Peel in the Context of Prostate Cancer

2.3.1. Identification of Secondary Metabolite Compounds

Secondary metabolite compounds contained in rambutan fruit peels are identified based on the results of Gas Chromatography-Mass Spectrometry (GC-MS) analysis obtained from the PubMed database.

2.3.2. Compound Structure Profiling

The molecular profiles of the compounds detected in the ethanol extract of rambutan peel were confirmed using the PubChem database (https://pubchem.ncbi.nlm.nih.gov/). The information obtained includes Simplified Molecular-Input Line-Entry System (SMILES) and three-dimensional (3D) structures of each compound for further analysis.

2.3.3. Prediction of Pharmacological Activity of Bioactive Compounds

The potential of bioactive compounds in rambutan peel extract as anticancer agents, especially against prostate cancer, was predicted using WAY2DRUG PASS (https://www.way2drug.com/PassOnline/index.php). This analysis uses the Structure-Activity Relationship (SAR) approach to compare target compounds with compounds known to have similar biological activities.

Table 1. SMILES profiles of rambutan peel compounds obtained from the PubChem database.

Code	Chemical Formulas	Compound Name	SMILES
C1	C9H12O	2-(2-Methylphenyl)ethanol	CC1=CC=CC=C1CCO
C2	C6H10O	1-Hexen-1-one	CCCCC=C=O
C4	C5H4O2	2-Furan-carboxaldehyde	C1=COC(=C1)C=O
C5	C5H10O3	Butanoic acid, 2-hydroxy-, methyl ester	CCC(C(=O)OC)O
C6	C6H6O2	5-Methylfuran-2-carbaldehyde	CC1=CC=C(O1)C=O
C7	C5H12O	2-Butanol, 3-methyl-, (S)-	CC(C)C(C)O
C8	C5H8O	2-Pentenal, (E)-	CC/C=C/C=O
C9	C5H6O2	3-Furanmethanol	C1=COC=C1CO
C10	C10H16	Myrcene	CC(=CCCC(=C)C=C)C
C11	C5H6O2	2-Cyclopenten-1-one, 2-hydroxy-	C1CC(=O)C(=C1)O
C13	C3H5NO	2-Propenamide	C=CC(=O)N
C14	C6H6O3	Levoglucosenone	C1[C@@H]2C=CC(=O)[C@H](O1)O2
C15	C5H4O3	5,6-Dihydropyran-2,5-dione	C1C=CC(=O)OC1=O
C16	C6H6O	Phenol (hydroxybenzene)	C1=CC=C(C=C1)O
C17	C6H6O3	2H-Pyran-2-one, 4-hydroxy-6-methyl-	CC1=CC(=CC(=O)O1)O
C18	C3H6O3	Dihydroxyacetone	C(C(=O)CO)O
C20	C4H8O2	3-Furanol, tetrahydro-	C1COCC1O
C21	C6H8O4	2,3-Dihydro-3,5-dihydroxy-6-methyl-4H-pyran-4-one	CC1=C(C(=O)C(CO1)O)O
C22	C3H8O3	1,2,3-Propanetriol (glycerol)	OCC(O)CO
C23	C14H14O	1,2-Diphenylethan-1-ol	C1=CC=C(C=C1)CC(C2=CC=CC=C2)O
C24	C12H24O2	Decanoic acid, ethyl ester	CCCCCCCCCC(=O)OCC
C25	C6H6O3	5-Hydroxymethylfurfural	C1=C(OC(=C1)C=O)CO
C26	C6H6O2	Catechol (1,2-benzenediol)	C1=CC=C(C(=C1)O)O
C27	C5H12O	Propane, 2-methoxy-2-methyl-	CC(C)(C)OC

2.3.4. Pharmacokinetic and Toxicity Evaluation

To assess the potential of developing compounds as drug candidates, pharmacokinetic analysis is carried out using ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) parameters. This assessment includes absorption in the circulatory system, distribution to target tissues, metabolism by enzymes, bodily excretion, and potential toxicity.

In addition, compound selection was done based on Lipinski's Rule of Five (Ro5) to assess the suitability of molecular characteristics to the desired pharmacokinetic properties in drug development. The SMILES notation of each compound was used as input data in the analysis using ADMETLab 3.0 (https://admetmesh.scbdd.com/service/evaluation/index) and Protox III (https://toxnew.charite.de/protox_III/index.php?site=compound_input) databases.

2.3.5. Protein Target Identification and Validation

Protein target identification was performed using Swiss Target Prediction (http://www.swisstargetprediction.ch/), SuperPred (https://prediction.charite.de/index.php), and Similarity Ensemble Approach (SEA) (https://sea16.docking.org/search). To obtain gene and protein data related to prostate cancer, the GeneCards database (https://www.genecards.org/) was used. Furthermore, mapping between prostate cancer disease targets and compounds in rambutan extract was performed using Draw Venn Diagram (https://bioinformatics.psb.ugent.be/webtools/Venn/) to identify relevant target intersection points. Protein target annotation was performed using ShinyGO 0.81 (http://bioinformatics.sdstate.edu/go/), focusing on biological pathways and molecular processes obtained from the Kyoto Encyclopedia of Genes and Genomes (KEGG) (https://www.genome.jp/kegg/).

2.3.6. Network Pharmacology Analysis

The interaction between the identified protein targets and prostate cancer was analyzed using the STRING Version 12.0 database (https://string-db.org/), with the selected organism being Homo sapiens (human). The analysis data from STRING was presented in TSV format and further processed using Cytoscape Version 3.10.3 (https://cytoscape.org/) to visualize the molecular network relationships formed.

3. Results and Discussion

3.1. Bioactive Compounds of Rambutan Peel

The analysis using Dr. Duke's databases yielded 28 compounds from rambutan fruit peel extract. These compounds were profiled for their SMILES representations through PubChem, as shown in Table 1,

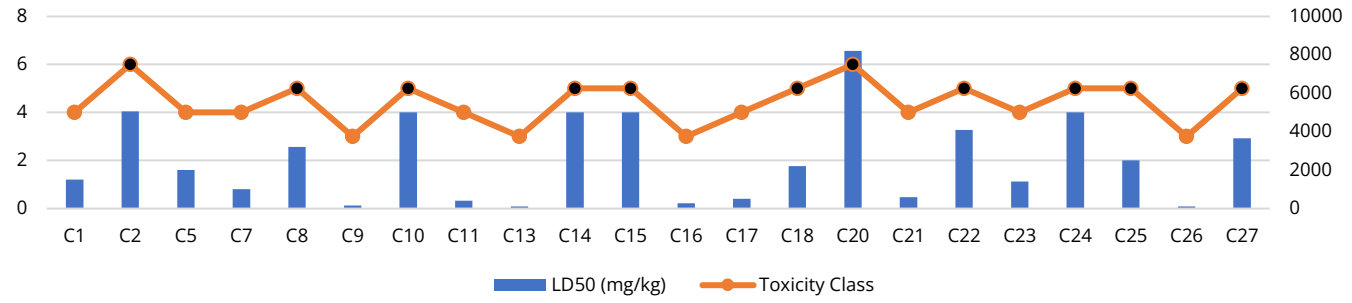

Figure 1. SAR-based prediction of TP53 expression enhancer.

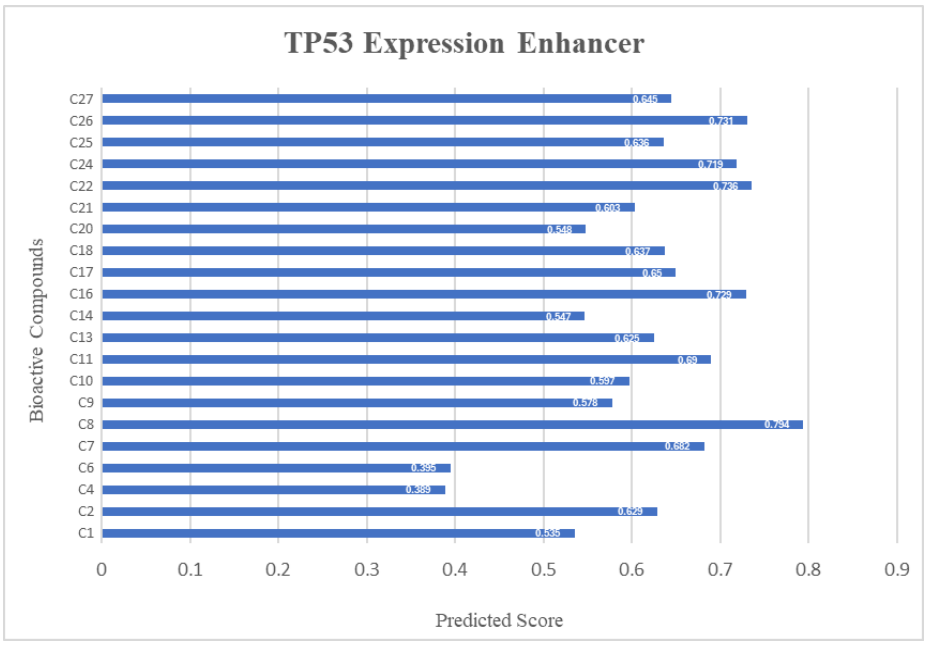

Figure 2. Prediction of toxicity based on LD50 and toxicity class.

serving as a standardized format for chemical and bioinformatics purposes.

3.2. Biological Activity Prediction

The SMILES profile of each compound predicted potential biological activity as a prostate anticancer agent, based on the Probability active (Pa) and Probability inactive (Pi) values. A Pa value ≥ 0.7 indicates a high likelihood of activity, which can be further validated through laboratory testing. A Pa value between 0.3 and 0.7 suggests moderate activity with an uncertain level of validation. In contrast, a Pa value ≤ 0.3 indicates very low activity as determined by both computational predictions and laboratory results [20, 34].

The assessment of prostate anticancer activity in rambutan fruit peel compounds was based on their relevance to prostate cancer, evaluated through three main parameters: inhibition of Androgen Receptor (AR) expression, induction of Tumor Protein 53 (TP53) expression, and stimulation of Nuclear Factor Erythroid 2 (NF-E2-related factor 2). Compounds with Pa values greater than 0.5 were considered to have significant biological potential.

Further analysis revealed that compound C3 (Acetic acid) displayed neither Pa nor Pi values, indicating the lack of predicted biological activity. Compounds C4 and C6 also exhibited low Pa values of 0.3, suggesting limited potential activity. The parameters utilized in this analysis, as shown in Figure 1, provide a foundation for evaluating the potential of rambutan peel compounds as effective prostate anticancer agents with significant molecular relevance.

3.3. Pharmacokinetic Evaluation and Drug Similarity Assessment

Pharmacokinetic assessment revealed that, of the 22 compounds examined, 11 compounds classified under toxicity classes V and VI—namely C2, C8, C10, C14, C15, C18, C20, C22, C24, C25, and C27—were selected for further analysis. These compounds are indicated by black dots in Figure 2.

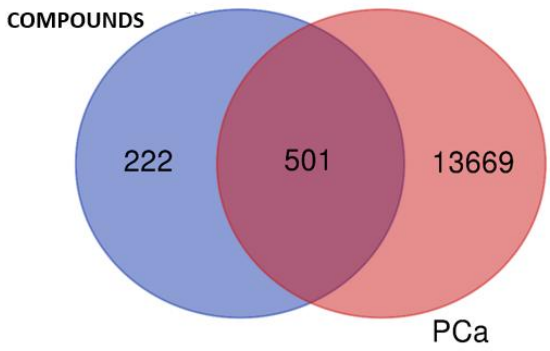

Figure 3. The intersection between rambutan peel extract and genes associated with PCa.

Table 2. Prostate cancer-related signaling pathways based on KEGG database analysis.

Pathways Code	Pathways Name
hsa01521	EGFR tyrosine kinase inhibitor resistance
hsa04066	HIF-1 signaling pathway
hsa04210	Apoptosis
hsa05205	Proteoglycans in cancer
hsa04024	cAMP signaling pathway
hsa05200	Pathways in cancer
hsa04010	MAPK signaling pathway
hsa04151	PI3K-Akt signaling pathway

3.4. Potential Protein Targets and Biological Pathways

Protein target compounds were collected from two web servers, SwissTarget Prediction and Similarity Ensemble Approach (SEA), and prostate cancer proteins as disease targets obtained from GeneCards. The analysis results in Figure 3 show that there are 501 nodes. This indicates that the proteins interact more than random proteins of equivalent size and degree distribution from the genome. This enrichment confirms that the proteins are at least biologically connected as a group.

3.5. Pharmacology Network Analysis

This network pharmacology-based study identified bioactive components in rambutan fruit peel extract that contribute to its potential as a prostate anticancer agent. Signaling pathway analysis, conducted using the KEGG database, revealed that key target proteins involved in the primary molecular mechanisms include the Epidermal Growth Factor Receptor (EGFR), Mitogen-Activated Protein Kinase (MAPK), apoptosis pathway, Hypoxia-Inducible Factor-1 (HIF-1) signaling, Cyclic Adenosine Monophosphate (cAMP), cancer pathways, proteoglycans in cancer, and the Phosphoinositide 3-Kinase/Protein Kinase B (PI3K-Akt) pathway, as detailed in Table 2.

Protein-protein interaction (PPI) data for all target proteins were compiled, visualized, and analyzed using Cytoscape to investigate the biological network (Figure 4). This analysis aimed to categorize the target proteins according to degree values and identify critical proteins within the network by evaluating parameters such as degree, betweenness centrality, and closeness centrality, which are standard metrics for assessing the roles of key proteins in biological networks.

The results of the PPI network analysis showed that 10 target proteins—SRC, GNAI1, PIK3CA, PIK3CD, MAPK1, MAPK3, AKT1, GNAI3, PRKCA, and HSP90AA1—are considered core proteins involved in prostate cancer. Among these, SRC exhibited a high overall score. SRC is a non-receptor tyrosine kinase that recruits intracellular signaling complexes through interactions with Src Homology 2 (SH2) and Src Homology 3 (SH3) domains. These proteins are crucial components in signal transduction from growth factor receptors and the regulation of cytoskeleton dynamics. Furthermore, SRC is involved in various processes that support tumorigenesis, including metastasis, invasion, cell adhesion, migration, survival, angiogenesis, and differentiation [19].

SRC influences multiple downstream pathways, including RAS/MAPK and PI3K/AKT, which are involved in signal transduction that regulates cell growth and interactions with the extracellular matrix [38]. Activation of SRC has been demonstrated to enhance cancer cell motility and contribute to metastatic progression, highlighting its significance in studies focused on inhibiting the invasion and migration processes in prostate cancer [39].

Additionally, several proteins, including AKT1, have been identified as playing key roles in various crucial biological pathways, such as resistance to EGFR tyrosine kinase inhibitors and the MAPK signaling pathway [40]. The HSP90AA1 protein contributes to drug resistance by inhibiting apoptosis [41]. This pathway is frequently activated by growth factors such as EGF and insulin and involves the PI3K pathway, which supports cancer cell survival and inhibits apoptosis. AKT1 accelerates cancer cell proliferation in prostate cancer and helps evade programmed cell death [42].

Resistance to EGFR tyrosine kinase inhibitors was selected as the primary pathway for activating rambutan peel's potential against prostate cancer, as this receptor is commonly mutated or overexpressed in various human cancers and serves as a major target in numerous cancer therapies focused on its signaling pathway [43]. EGFR is oncogenic in supporting cancer cell survival independent of its tyrosine kinase activity. Therefore,

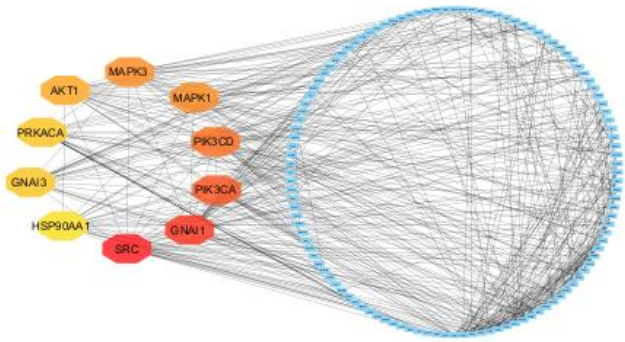

Figure 4. Visualization of PPI target of rambutan peel extract on disease proteins.

targeting the kinase-independent functions of EGFR could present a promising strategy to overcome resistance to existing EGFR inhibitors in cancer therapy [44].

SRC and EGFR mutually enhance each other's activity in tumorigenesis, and the inhibition of both targets can attenuate or prevent EGF-mediated cancer progression [45]. Targeting EGFR presents a promising therapeutic strategy for prostate cancer, as tyrosine kinase inhibitors can disrupt signaling pathways that facilitate tumorigenesis and metastasis, reduce cancer cell proliferation, and enhance the efficacy of other therapeutic approaches [43, 44].

4. Conclusions

This study highlights the potential of rambutan peel as a promising prostate anticancer agent. With the growing prevalence of prostate cancer and the limitations of current treatment options, natural compounds offer an important avenue for the development of more effective therapies. The identification of target proteins, including SRC, GNAI1, PIK3CA, PIK3CD, MAPK1, MAPK3, AKT1, GNAI3, PRKCA, and HSP90AA1, through resistance to EGFR tyrosine kinase inhibitors underscores the therapeutic relevance of rambutan peel compounds. Notably, SRC emerged as a key target, with its significant role in disrupting tumorigenic signaling pathways, inhibiting cancer cell proliferation, and enhancing the therapeutic response. These findings provide a foundation for further exploration of rambutan peel as a potential treatment strategy for prostate cancer.

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