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Exploring the potential role of ginsenoside Rd in the treatment of prostate cancer based on network pharmacology

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ABSTRACT: *Ginsenoside Rd has strong anticancer properties, but fewer specific targets have been identified for its effect on prostate cancer (PCa). The potential role of ginsenoside Rd in the treatment of prostate cancer was explored by network pharmacology and molecular docking techniques. A total of 496 targets were obtained from the intersection of ginsenoside Rd and prostate cancer, with KEGG enrichment analysis generating 228 entries, and GO enrichment analysis generating 3828 entries, including the negative regulation of cell population proliferation, lesion adhesion, and protein kinase activity. Ninety important targets were screened by protein-protein interaction (PPI) network, and molecular docking was used to obtain eight key targets GSK3B, PARP1, H3-3B, GAPDH, ALB, BCL2, MMP9, and AKT1 that bind well to ginsenoside Rd, with binding energies ≤ -10 kcal/mol. H3-3B, BCL2, and AKT1 were further screened as core targets of ginsenoside Rd affecting PCa by immune cell infiltration, mRNA levels, and protein expression in prostate tissues of PCa patients and healthy individuals. Ginsenoside Rd acts on H3-3B, BCL2, and AKT1 to curb prostate cancer development by affecting the PI3K-Akt signaling pathway, negative regulation of cell population proliferation, positive regulation of programmed cell death, and affecting the activity of related enzymes.*

KEY WARDS: *ginsenoside Rd, prostate cancer, Network Pharmacology, molecular docking, protein-protein interaction networks*

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I. INTRODUCTION

Prostate cancer is a highly heterogeneous cancer that is the most common non-skin cancer [1] occurring in male patients worldwide and is the second most common solid organ cancer after lung cancer in men [2][3]. Because of its high prevalence, it contributes significantly to the global increase in male mortality [4].

Studies have shown that ginsenosides purified from ginseng have anticancer effects [5]. Ginsenoside Rd has the strongest ability to induce cancer cell death among diol-type ginsenosides [6] and has strong cancer-inhibitory ability. Rd significantly increased the expression of apoptosis-related proteins such as Caspase-3 and Caspase-9, and induced apoptosis to inhibit the proliferation of gastric cancer cells [7]. Rd was able to reduce migration, invasion, and clone formation of colorectal cancer cells by affecting the epidermal growth factor receptor signaling axis to inhibit their metastasis [8]. Rd exerted anti-tumor effects, including miR-144-5p up-regulation and TLR2 down-regulation to inhibit glioblastoma cell viability [9]. All these indicate the existence of considerable potential anti-tumor value of ginsenoside Rd with anti-prostate cancer potential.

The current mainstream treatment modalities for prostate cancer have a high complication rate [10], and the presence of drug resistance hampers their therapeutic progress. There is an urgent need to find drug-adjuvant therapies to provide a better prognosis for prostate cancer patients. The anticancer properties of ginsenoside Rd are expected to assist in the treatment of prostate cancer. However, traditional Chinese medicine has a "multi-component, multi-target, multi-path" effect, which ensures synergistic effects by regulating the

biological network of the organism, and it is difficult to detect the mechanism of action of traditional Chinese medicine through conventional experiments, so the use of data mining is conducive to comprehensively analyzing the targets and pathways of ginsenoside Rd's action in prostate cancer. In this study, we combined information from several medical disease-related databases and relied on network pharmacology to establish the Rd-prostate cancer target interactions network, molecular docking to excavate the key targets of ginsenoside Rd acting on prostate cancer, while investigated the relationship between the key targets and immune cell infiltration, to explore the mechanism of ginsenoside Rd in the treatment of prostate cancer, to prove the potential value of ginsenoside Rd in the treatment of prostate cancer.

II. MATERIAL AND METHODS

2.1 Acquisition of ginsenoside Rd-PCa common target

Using "ginsenoside Rd" as the keyword, the ginsenoside Rd-related targets were obtained from the BATMAN-TCM 2.0 database (http://bionet.ncpsb.org.cn/batman-tcm/)[11], GeneCards database (https://www.genecards.org/) [12], and PharmMapper database (https://www.lilab-ecust.cn/pharmmapper/index.html [13]) to obtain ginsenoside Rd-related targets, respectively. The obtained results were converted into corresponding genes through the UniProt database (https://www.uniprot.org/) [14].

The ETCM database (http://www.tcmip.cn/ETCM/) [15], DisGeNet database (https://disgenet.com/) [16], and MalaCards database (http://www.tcmip.cn/ETCM/) [17] were used to obtain prostate cancer-related targets using the keyword "Prostate Cancer".

The ginsenoside Rd and prostate cancer target sums obtained were taken as intersections and visualized using the Venny 2.1.0 tool (https://bioinfogp.cnb.csic.es/tools/venny/) to obtain the targets of ginsenoside Rd interacting with prostate cancer, respectively.

2.2 ***GO/KEGG enrichment analysis***

The intersecting target of ginsenoside Rd with prostate cancer could be a potential destination target for therapy, which was imported into the Metascape database (https://metascape.org/gp/index.html) [18] for biological process (BP), cellular component (CC), molecular function (MF), and KEGG pathway analysis. The results were visualized using the “matplotlib” in Python 3.11.5 and the “ggplot2” package in R 4.3.3.

2.3 Building protein-protein interaction networks

Protein-protein interaction networks were constructed based on the intersecting targets of ginsenoside Rd and prostate cancer using the STRING database (https://cn.string-db.org/) [19] and imported into Cytoscape 3.10.1 software. The targets were visualized using the Degree Centrality algorithm according to "Degree>104" to visualize the targets.

2.4 Molecular docking

Structural information of ginsenoside Rd was obtained in the PubChem database (https://pubchem.ncbi.nlm.nih.gov/) [20]. MMFF94 force field was applied to molecularly dock the targets obtained from PPI screening with ginsenoside Rd. The crystal structures of the targets were all obtained from the PDB database (https://www.rcsb.org/) [21], and the ligands were topologically optimized using AutoDock Vina (http://vina.scripps.edu/) [22] for hydrogenation and removal of solvent molecules, then docked to the targets. BIOVIA Discovery Studio 2019 visualized the results.

2.5 Relevant expression validation of key targets

The GEPIA 2 database (http://gepia2.cancer-pku.cn/#index) [23] was used to explore the comparison of the changes in transcript levels of key target mRNAs in the aim tissues between prostate cancer patients and healthy individuals in vivo. The TIMER database (http://timer2.compbio.cn/timer1/) [24] was used to elucidate potential associations between core targets and levels of immune infiltration in the immune microenvironment. Immunohistochemically stained sections of target tissues from prostate cancer patients and healthy individuals were compared in vivo using the HPA database (https://www.proteinatlas.org/) [25] to analyze differences in expression levels of core target proteins.

III. RESULTS AND DISCUSSIONS

Using "ginsenoside Rd" as the keyword, the ginsenoside Rd targets were de-emphasized by three databases: BATMAN-TCM 2.0, GeneCards, and PharmMapper (Table 1). Finally, 2009 ginsenoside Rd-related targets were obtained. Using "prostate cancer" as the keyword, three databases, ETCM, DisGeNet, and MalaCards, were used to count the de-emphasis of prostate cancer targets (Table 1). This resulted in 2,281 prostate cancer-related targets. Combined the results of drug targets and disease targets in the database, the final

496 intersecting targets obtained as potential targets for Rd treatment of prostate cancer were entered into the analysis of relevant pathway enrichment (Fig. 1).

***Table II*.Number of ginsenoside Rd targets and number of prostate cancer targets from the online database**

Database names	Number of elements	Number of unique elements
BATMAN-TCM 2.0	30	14
GeneCards	1785	1694
PharmMapper	290	207
ETCM	71	11
DisGeNet	46	7
MalaCards	2263	2172

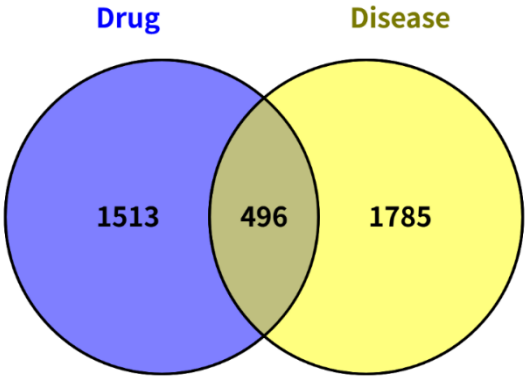

Figure 1: Target intersection of ginsenoside Rd with prostate cancer.

KEGG pathway enrichment analysis involved 228 signaling pathways, visualizing the top 10 pathways (Fig. 2A), which in descending order of P-value included pathways in cancer, lipid and atherosclerosis, hepatitis B, apoptosis, prostate cancer, Kaposi sarcoma-associated herpesvirus infection, Epstein-Barr virus infection, human cytomegalovirus infection, viral carcinogenesis, and PI3K-Akt signaling pathway.

GO enrichment analysis showed that BP involved 3226 entries, CC involved 219 entries, and MF involved 383 entries, and the top 10 entries of each were selected for visualization (Fig. 2B). BP included cellular response to hormone stimulus, negative regulation of cell population proliferation, positive regulation of programmed cell death and so on. CC included perinuclear region of cytoplasm, focal adhesion, cell-substrate junction and so on. MF included phosphotransferase activity-alcohol group as acceptor, kinase activity, protein kinase activity and so on.

The KEGG pathway shows that ginsenoside Rd is associated with multiple viral infection mechanisms and indeed has a significant effect on prostate cancer. Pathways in cancer, apoptosis, and the PI3K-Akt signaling pathway may serve as a focused pathway for intervention. GO enrichment analyses, especially the negative regulation of cell population proliferation, positive regulation of programmed cell death, and the influence of related enzyme activities may be one of the ways ginsenoside Rd regulates prostate cancer.

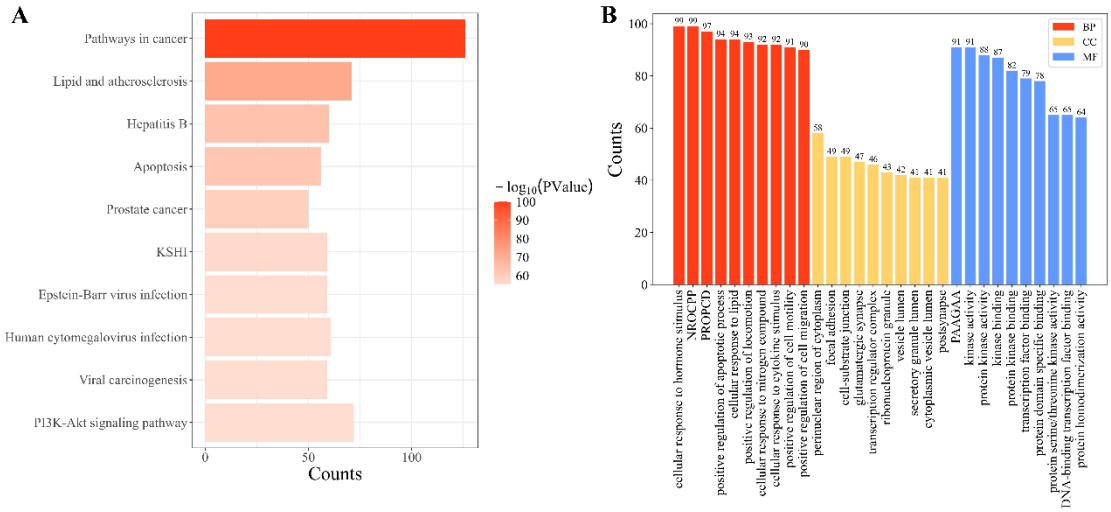

Figure 2: Enrichment analysis of intersecting targets ((A) KEGG pathway enrichment analysis of ginsenoside Rd in prostate cancer (Kaposi sarcoma-associated herpesvirus infection(KSHI)); (B) GO functional enrichment analysis of ginsenoside Rd in prostate cancer (negative regulation of cell population proliferation(NROCPP)、positive regulation of programmed cell death(PROPCD)、phosphotransferase activity, alcohol group as acceptor(PAAGAA))).

The obtained 496 ginsenoside Rd common targets with prostate cancer were imported into the STRING database to obtain the PPI network. A higher value of Degree indicates a higher density of inter-target connections, the more the target interacts with other targets, and the higher the probability of the target being predicted as a core target. Thus, visualizing the protein interaction network with "Degree>104", 90 nodes and 3284 edges were obtained. Among them (Fig. 3), GAPDH, AKT1, BCL2, ALB, GSK3B, PARP1, H3-3B, and MMP9 have larger Degree values of 323, 312, 231, 224, 187, 182, 175, and 173, respectively. It is proposed that molecular docking will be used to further analyze the interactions of ginsenoside Rd with these targets. A larger node indicates a larger Degree value of the target, and the targets with larger nodes in Figure 3 are closely related to the pathway of cancer, PI3K-Akt signaling pathway, cell proliferation, apoptosis, etc. This verifies the results of the enrichment analysis of the intersecting targets of ginsenoside Rd and prostate cancer in Figure 2, and provides a basis for the specific target function of ginsenoside Rd in prostate cancer.

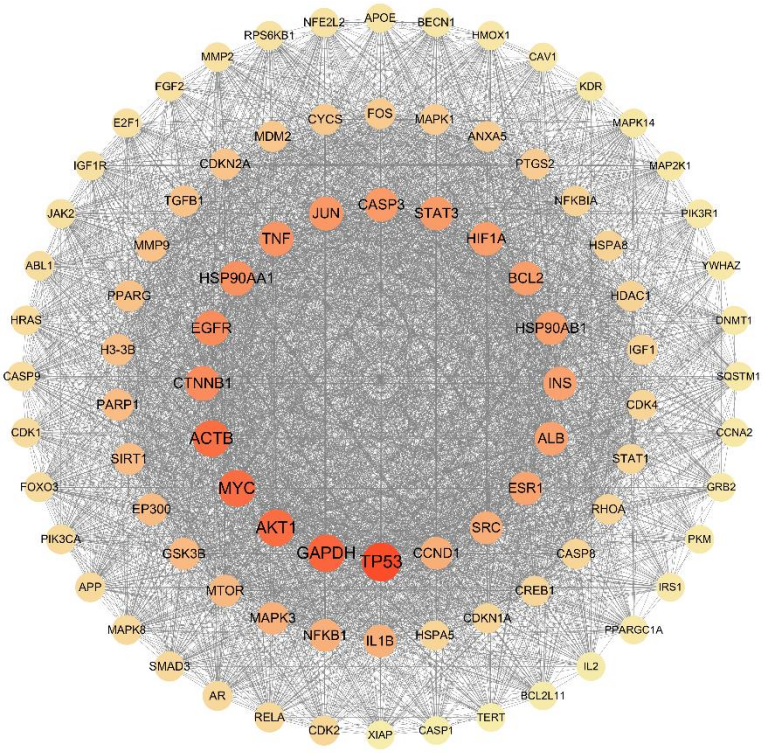

Figure 3: PPIs of important potential targets of ginsenoside Rd in the treatment of prostate cancer.

The binding of drug-disease strong correlation nodes with "degree > 150" in the PPI network to ginsenoside Rd was assessed by molecular docking. The aim is to obtain prostate cancer targets that bind better to ginsenoside Rd. Based on binding free energy calculations, there were eight ginsenoside Rd-interacting prostate cancer targets with Binding affinity < -10 kcal/mol, namely GSK3B, PARP1, H3-3B, GAPDH, ALB, BCL2, MMP9, and AKT1 (Table 2). The lower free energy of binding indicates more stable binding, and these eight targets bind well to ginsenoside Rd.

GSK3B is a conserved serine/threonine kinase that acts as a tumor suppressor, affecting the cell cycle and DNA repair by influencing the phosphorylation of DNA repair factors and their binding to chromatin, while GSK-3β inhibitors target malignant tumors [26]. PARP1 participates in homology repair (HR) and base excision repair (BER) signaling pathways that can target DNA repair mechanisms to destroy cancer cell viability, while DNA repair inhibitors (PARPi) have a vast prospect for adjuvant cancer therapy [27]. H3-3B is a member of a family of proteins that fulfil the function of binding DNA and condensing it into chromatin, and changes in its gene expression can serve as a possible prognostic biomarker for pre-metastatic colorectal cancer [28]. GAPDH is associated with DNA integrity, nuclear tRNA export, and post-transcriptional regulation of tumor cell mRNAs, while cancer patients affected by GAPDH have a poor prognosis [29].

ALB transports a variety of endogenous and exogenous substances, interferes with endocrine signaling pathways, and is implicated in the systemic effects of endocrine disruptors on cancer progression [30]. BCL2 is up-regulated in neuroendocrine carcinomas and can be used as a destination target to participate in apoptosis-resistant pathways in combination with treatment of AR non-dependent denervation-resistant prostate cancer (CRPC) to enhance cancer cell apoptosis [31]. MMP9 affects tumor cell metastasis and can be involved in cancer prognosis as a biomarker, while overexpression is associated with poor survival, large tumor size, and lymph node metastasis in breast cancer patients [32]. As a hub of the PI3K/AKT signaling pathway, AKT1 kinase activity is significantly increased in prostate, breast, and ovarian cancers, while the inhibition of AKT1 kinase activity inhibits prostate cancer cell function and tumor development in vitro [33][34]. The important role of the eight targets in fighting cancer suggests that ginsenoside Rd may exert corresponding anticancer effects by binding well to them.

Hydrophobic and hydrogen bonding forces are the main forces involved in the docking formation of ginsenoside Rd and eight core prostate cancer target molecules (Fig. 4). Val70, Lys85, Cys199, and Pro258 of GSK3B protein (Fig. 5A) have strong hydrophobic interactions with ginsenoside Rd. Leu108, His201, Arg204, Arg217, Ala219, Pro220, Tyr235, Tyr246, and His248 of the PARP1 protein (Fig. 5B) have strong hydrophobic interactions with the ginsenoside Rd. Met84, Lys85, and Tyr88 of the H3-3B protein (Fig. 5C) have a strong hydrophobic interaction with ginsenoside Rd. Ile14, Phe37, and Val101 of the GAPDH protein (Fig. 5D) have a

strong hydrophobic interaction with ginsenoside Rd. Leu115, Arg145, His146, Arg186, and Lys190 of the ALB protein (Fig. 5E) have a strong hydrophobic interaction with the ginsenoside Rd. Phe101, Arg104, Leu134, Arg143, and Ala146 of BCL2 protein (Fig. 5F) have strong hydrophobic interactions with ginsenoside Rd. Leu39, Leu44, Arg95, and Pro97 of the MMP9 protein (Fig. 5G) have a strong hydrophobic interaction with the ginsenoside Rd. Phe161, Lys189, and Leu295 of the AKT1 protein (Fig. 5H) have a strong hydrophobic interaction with ginsenoside Rd. The interaction sites of each protein with the drug contain some non-polar hydrophobic amino acids (Leu, Ala, Ile, Gly, Val, etc.) or aromatic amino acids (Phe, etc.), which produce strong π-alkyl hydrophobic forces, etc. Its hydrophobic property promotes stable binding between ginsenoside Rd and the target.

Meanwhile, the presence of polar amino acids such as Ser, Thr, and Asn allowed the formation of hydrogen bonds between ginsenoside Rd and the core targets of prostate cancer (e.g. Asn64, Ser66, Asp181, Lys183, Ser203, Ser219, Tyr221, Pro255, and Asp264 of the GSK3B protein (Fig. 4A) form a hydrogen bond with the ginsenoside Rd). Despite the presence of some adverse forces, these suggest that ginsenoside Rd binds well to the core target. The strong docking binding affinity can indicate that ginsenoside Rd may bind to the core target and thus exert an anticancer effect. It also demonstrates the reliability of a network pharmacological screen for key targets of ginsenoside Rd for the treatment of prostate cancer.

Table II: Docking binding energy of ginsenoside Rd intercalating with prostate cancer targets

Targets	Protein names	PDB ID	Resolution (Å)	Binding affinity (kcal/mol)
GSK3B	Glycogen synthase kinase-3 beta	1PYX	2.4	-11.1
PARP1	Poly [ADP-ribose] polymerase 1	3GJW	2.3	-10.7
H3-3B	Histone H3.3	5B32	2.35	-10.4
GAPDH	Glyceraldehyde-3-phosphate dehydrogenase	1U8F	1.75	-10.3
ALB	Albumin	1E7A	2.2	-10.2
BCL2	Apoptosis regulator Bcl-2	4MAN	2.07	-10.2
MMP9	Matrix metalloproteinase-9	1L6J	2.5	-10.1
AKT1	RAC-alpha serine/threonine-protein kinase	3MVH	2.01	-10.0

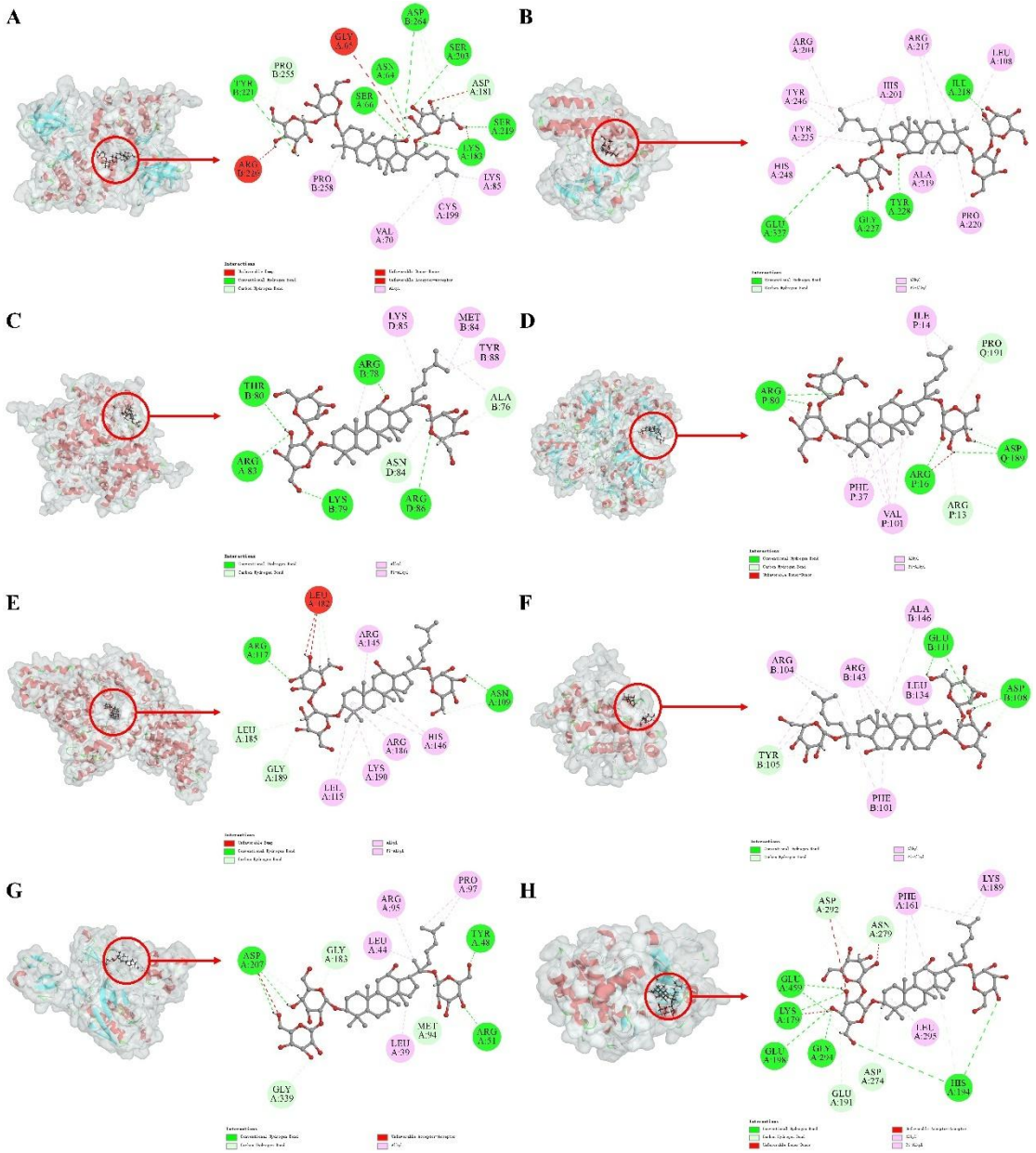

Figure 4: Molecular docking interactions of ginsenoside Rd with core targets ((A) GSK3B; (B) PARP1; (C) H3-3B; (D) GAPDH; (E) ALB; (F) BCL2; (G) MMP9; (H) AKT1).

The GEPIA2 database integrates data from the transcriptome sequencing of more than 30 solid tumors and corresponding adjacent normal tissues using RNA-Seq technology from the Cancer Genome Atlas (TCGA) project [35], and data from 44 tissues of 449 living healthy donors from the Genotype-Tissue Expression (GTEx) project [36] to analyze the mRNA transcription of eight targets in PCa tissues and normal tissues in the molecular docking results (Fig. 5). H3-3B, BCL2, MMP9, and AKT1 target mRNAs showed more significant changes in PCa tissues and normal tissues. H3-3B, BCL2, MMP9, and AKT1 are proposed to be used as key targets for continued validation in prostate cancer. In particular, BCL2 mRNA levels were significantly higher ($P < 0.01$) and MMP9 mRNA levels were significantly lower ($P < 0.01$) in tissues intended for prostate cancer patients compared to tissues from healthy individuals.

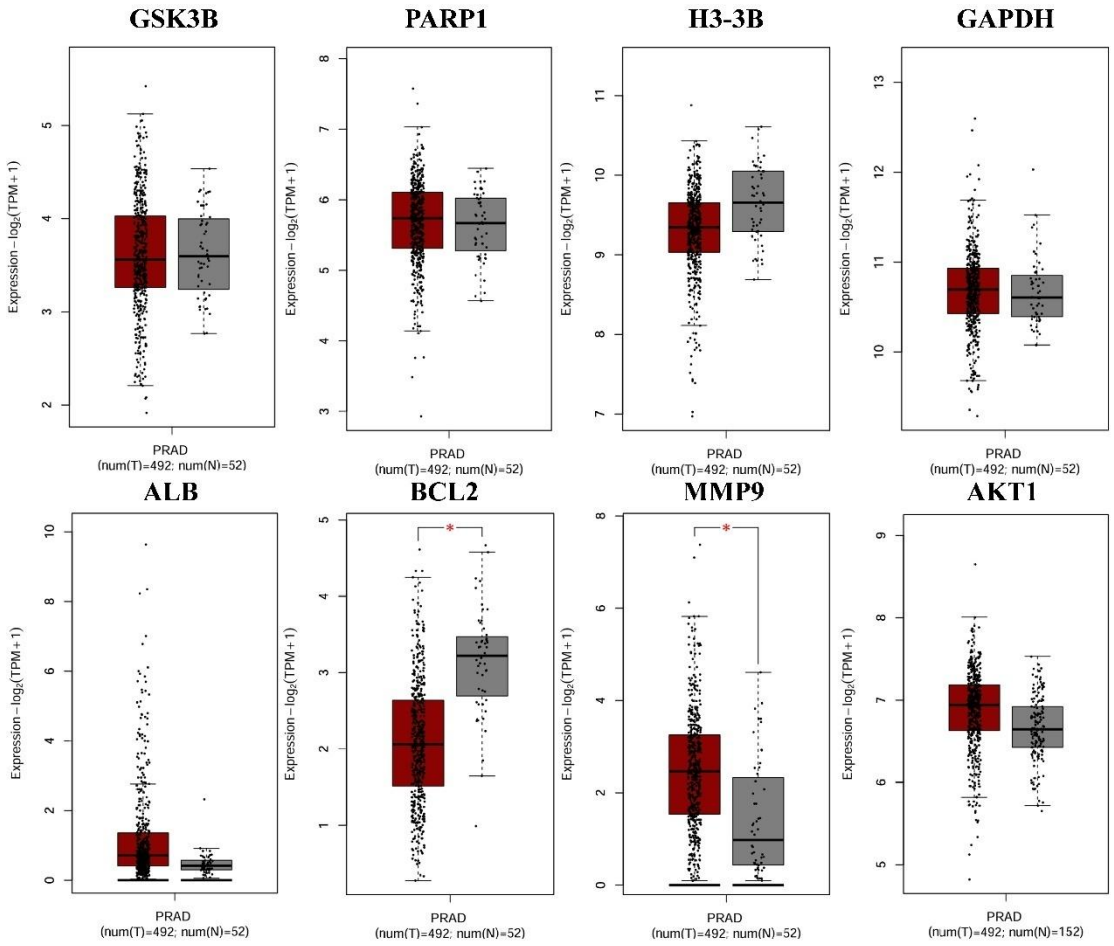

Figure 5: mRNA transcript levels of core target genes in PCa and normal tissues (red represents PCa tissue, grey represents normal tissue).

The TIMER database uses six algorithms, including CIBERSORT, EPIC, TIDE, and XCELL, to deconvolute the TPM matrix of TCGA-GTEx and presents the transcriptome data in TCGA/GTEx as a spatial-quantitative map of immune cells in the tumor microenvironment, which reveals the relationship between the target and potential immunosuppression through the effect of targets on the tumor immune microenvironment [24].

It analyzed the relationship between H3-3B, BCL2, MMP9, AKT1 and the infiltration of six types of immune cells: B cells, CD8+ T cells, CD4+ T cells, macrophages, neutrophils, and dendritic cells (Fig. 6). H3-3B (i.e. H3F3B) was negatively correlated with purity and positively correlated with infiltration of B cells, CD8+ T cells, CD4+ T cells, macrophages, neutrophils, and dendritic cells. BCL2 was negatively correlated with purity and positively correlated with infiltration of B cells, CD8+ T cells, CD4+ T cells, macrophages, neutrophils, and dendritic cells. MMP9 was negatively correlated with purity and positively correlated with infiltration of B cells, CD8+ T cells, CD4+ T cells, macrophages, neutrophils, and dendritic cells. AKT1 was positively correlated with infiltration of B cells, CD8+ T cells, macrophages, neutrophils, and dendritic cells.

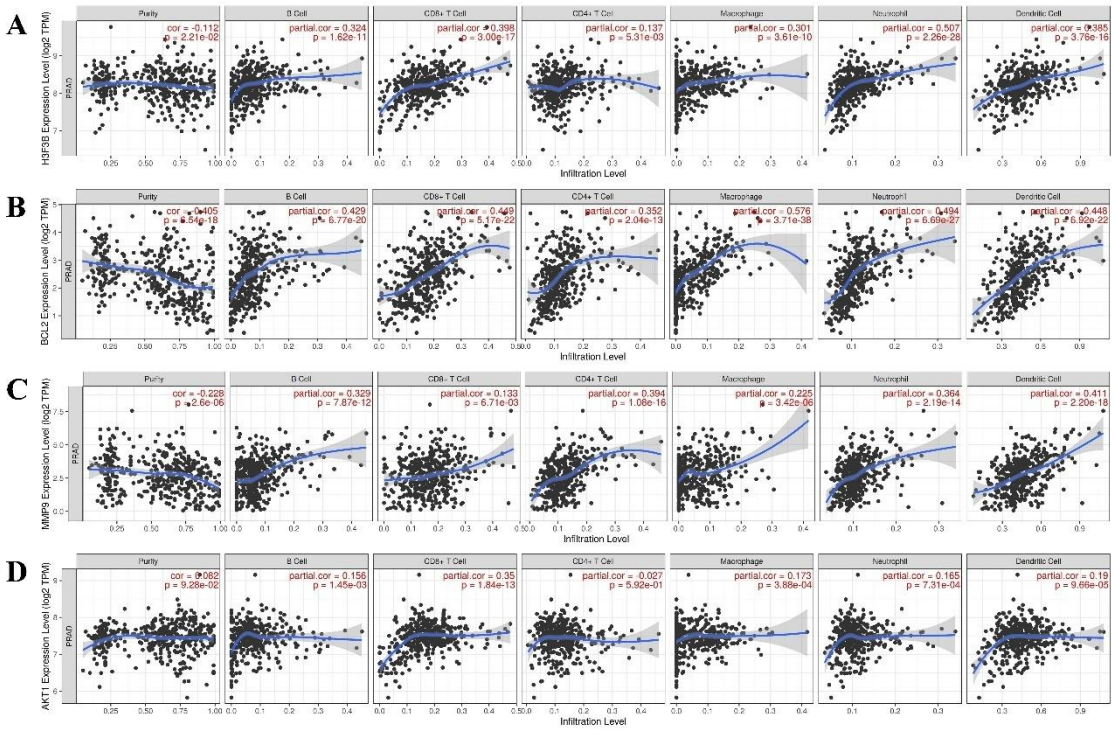

Figure 6: Relationship between H3-3B, BCL2, MMP9, AKT1 and infiltration of six immune cells ((A) H3F3B (i.e., H3-3B); (B) BCL2; (C) MMP9; (D) AKT1).

The HPA database stores the results of high-throughput immunohistochemistry (IHC) processing of tissue microarrays (TMAs) made from normal human and tumor tissues, which can locate how much of the target protein is expressed in the diseased/normal tissues and exactly where it is expressed [25]. Expression levels of four key target proteins were compared by HPA database analysis. As shown in Figure 7, compared with normal prostate tissues, the expression levels of H3-3B and AKT1 were elevated in the prostate tissues of PCa patients, while the expression levels of BCL2 were decreased in the prostate tissues of PCa patients. It can be seen that H3-3B, AKT1, and BCL2 are the key targets of ginsenoside Rd interactions for prostate cancer obtained from the final screening.

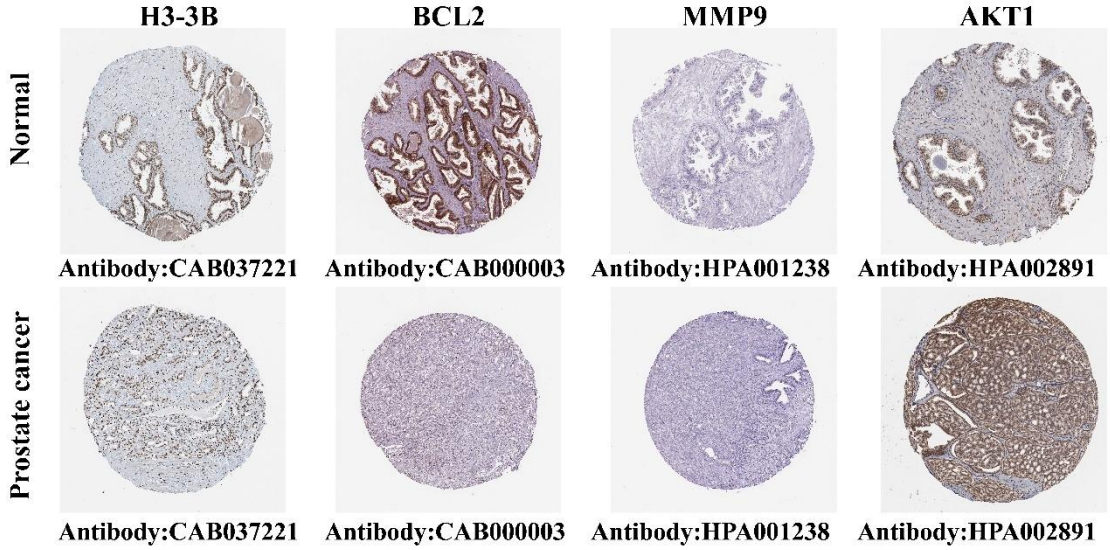

Figure 7: Immunohistochemical images of protein expression levels of core target genes in PCa tissue and normal prostate tissue.

IV. CONCLUSION

Eight targets were obtained from 496 intersecting targets of ginsenoside Rd with prostate cancer by network pharmacology and molecular docking. GSK3B, PARP1, H3-3B, GAPDH, ALB, BCL2, MMP9, and AKT1 were involved in the PI3K-Akt signaling pathway, the negative regulation of cell population proliferation, the positive regulation of programmed cell death, and the influence of related enzyme activities, etc. They affected the proliferation and apoptosis of tumor cells. Ginsenoside Rd exerted its anticancer effects by binding well to these eight targets. Bioinformatic analysis of transcript levels, protein expression of the targets in normal human tissues and PCa tumor tissues, while immune cell infiltration further identified H3-3B, AKT1, and BCL2 as the core targets of ginsenoside Rd in prostate cancer. These systematically elucidated the potential mechanism of ginsenoside Rd against prostate cancer. This study provides a new perspective for ginsenoside Rd against prostate cancer, and provides some theoretical support for further experimental validation of ginsenoside Rd in adjuvant treatment of prostate cancer.

V. ACKNOWLEDGMENTS

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REFERENCES

[1]. Wang G, Zhao D, Spring DJ, DePinho RA. Genetics and biology of prostate cancer. Genes Dev. 2018 Sep 1;32(17-18):1105-1140.
[2]. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015 Mar 1;136(5):E359-86.
[3]. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018 Nov;68(6):394-424.
[4]. Sekhoacha M, Riet K, Motloung P, Gumenku L, Adegoke A, Mashele S. Prostate Cancer Review: Genetics, Diagnosis, Treatment Options, and Alternative Approaches. Molecules. 2022 Sep 5;27(17):5730.
[5]. Yang Y, Nan Y, Du Y, Liu W, Ning N, Chen G, Gu Q, Yuan L. Ginsenosides in cancer: Proliferation, metastasis, and drug resistance. Biomed Pharmacother. 2024 Aug;177:117049.
[6]. Kim YJ, Yamabe N, Choi P, Lee JW, Ham J, Kang KS. Efficient thermal deglycosylation of ginsenoside Rd and its contribution to the improved anticancer activity of ginseng. J Agric Food Chem. 2013 Sep 25;61(38):9185-91.
[7]. Tian YZ, Liu YP, Tian SC, Ge SY, Wu YJ, Zhang BL. Antitumor activity of ginsenoside Rd in gastric cancer via up-regulation of Caspase-3 and Caspase-9. Pharmazie. 2020 Apr 6;75(4):147-150.
[8]. Phi LTH, Sari IN, Wijaya YT, Kim KS, Park K, Cho AE, Kwon HY. Ginsenoside Rd Inhibits the Metastasis of Colorectal Cancer via Epidermal Growth Factor Receptor Signaling Axis. IUBMB Life. 2019 May;71(5):601-610.
[9]. Liu GM, Lu TC, Sun ML, Jia WY, Ji X, Luo YG. Ginsenoside Rd Inhibits Glioblastoma Cell Proliferation by Up-Regulating the Expression of miR-144-5p. Biol Pharm Bull. 2020;43(10):1534-1541.
[10]. Desai MM, Cacciamani GE, Gill K, Zhang J, Liu L, Abreu A, Gill IS. Trends in Incidence of Metastatic Prostate Cancer in the US. JAMA Netw Open. 2022 Mar 1;5(3):e222246.
[11]. Kong X, Liu C, Zhang Z, Cheng M, Mei Z, Li X, Liu P, Diao L, Ma Y, Jiang P, Kong X, Nie S, Guo Y, Wang Z, Zhang X, Wang Y, Tang L, Guo S, Liu Z, Li D. BATMAN-TCM 2.0: an enhanced integrative database for known and predicted interactions between traditional Chinese medicine ingredients and target proteins. Nucleic Acids Res. 2024 Jan 5;52(D1):D1110-D1120.
[12]. Stelzer G, Rosen N, Plaschkes I, Zimmerman S, Twik M, Fishilevich S, Stein TI, Nudel R, Lieder I, Mazor Y, Kaplan S, Dahary D, Warshawsky D, Guan-Golan Y, Kohn A, Rappaport N, Safran M, Lancet D. The GeneCards Suite: From Gene Data Mining to Disease Genome Sequence Analyses. Curr Protoc Bioinformatics. 2016 Jun 20;54:1.30.1-1.30.33.
[13]. Wang X, Shen Y, Wang S, Li S, Zhang W, Liu X, Lai L, Pei J, Li H. PharmMapper 2017 update: a web server for potential drug target identification with a comprehensive target pharmacophore database. Nucleic Acids Res. 2017 Jul 3;45(W1):W356-W360.
[14]. Ahmad S, Jose da Costa Gonzales L, Bowler-Barnett EH, Rice DL, Kim M, Wijerathne S, Luciani A, Kandasaamy S, Luo J, Watkins X, Turner E, Martin MJ; UniProt Consortium. The UniProt website API: facilitating programmatic access to protein knowledge. Nucleic Acids Res. 2025 Jul 7;53(W1):W547-W553.
[15]. Xu HY, Zhang YQ, Liu ZM, Chen T, Lv CY, Tang SH, Zhang XB, Zhang W, Li ZY, Zhou RR, Yang HJ, Wang XJ, Huang LQ. ETCM: an encyclopaedia of traditional Chinese medicine. Nucleic Acids Res. 2019 Jan 8;47(D1):D976-D982.
[16]. Piñero J, Ramírez-Anguita JM, Saüch-Pitarch J, Ronzano F, Centeno E, Sanz F, Furlong LI. The DisGeNET knowledge platform for disease genomics: 2019 update. Nucleic Acids Res. 2020 Jan 8;48(D1):D845-D855.
[17]. Rappaport N, Twik M, Plaschkes I, Nudel R, Iny Stein T, Levitt J, Gershoni M, Morrey CP, Safran M, Lancet D. MalaCards: an amalgamated human disease compendium with diverse clinical and genetic annotation and structured search. Nucleic Acids Res. 2017 Jan 4;45(D1):D877-D887.
[18]. Zhou Y, Zhou B, Pache L, Chang M, Khodabakhshi AH, Tanaseichuk O, Benner C, Chanda SK. Metascape provides a biologist-oriented resource for the analysis of systems-level datasets. Nat Commun. 2019 Apr 3;10(1):1523.
[19]. Szklarczyk D, Kirsch R, Koutrouli M, Nastou K, Mehryary F, Hachilif R, Gable AL, Fang T, Doncheva NT, Pyysalo S, Bork P, Jensen LJ, von Mering C. The STRING database in 2023: protein-protein association networks and functional enrichment analyses for any sequenced genome of interest. Nucleic Acids Res. 2023 Jan 6;51(D1):D638-D646.
[20]. Kim S, Chen J, Cheng T, Gindulyte A, He J, He S, Li Q, Shoemaker BA, Thiessen PA, Yu B, Zaslavsky L, Zhang J, Bolton EE. PubChem 2025 update. Nucleic Acids Res. 2025 Jan 6;53(D1):D1516-D1525.
[21]. Burley SK, Bhatt R, Bhikadiya C, Bi C, Biester A, Biswas P, Bittrich S, Blaumann S, Brown R, Chao H, Chithari VR, Craig PA, Crichlow GV, Duarte JM, Dutta S, Feng Z, Flatt JW, Ghosh S, Goodsell DS, Green RK, Guranovic V, Henry J, Hudson BP, Joy M, Kaelber JT, Khokhriakov I, Lai JS, Lawson CL, Liang Y, Myers-Turnbull D, Peisach E, Persikova I, Piehl DW, Pingale A, Rose Y, Sagendorf J, Sali A, Segura J, Sekharan M, Shao C, Smith J, Trumbull M, Vallat B, Voigt M, Webb B, Whetstone S, Wu-Wu A,

Xing T, Young JY, Zalevsky A, Zardecki C. Updated resources for exploring experimentally-determined PDB structures and Computed Structure Models at the RCSB Protein Data Bank. Nucleic Acids Res. 2025 Jan 6;53(D1):D564-D574.
[22]. Trott O, Olson AJ. AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading. J Comput Chem. 2010 Jan 30;31(2):455-61.
[23]. Tang Z, Kang B, Li C, Chen T, Zhang Z. GEPIA2: an enhanced web server for large-scale expression profiling and interactive analysis. Nucleic Acids Res. 2019 Jul 2;47(W1):W556-W560.
[24]. Li T, Fu J, Zeng Z, Cohen D, Li J, Chen Q, Li B, Liu XS. TIMER2.0 for analysis of tumor-infiltrating immune cells. Nucleic Acids Res. 2020 Jul 2;48(W1):W509-W514.
[25]. Uhlén M, Fagerberg L, Hallström BM, Lindskog C, Oksvold P, Mardinoglu A, Sivertsson Å, Kampf C, Sjöstedt E, Asplund A, Olsson I, Edlund K, Lundberg E, Navani S, Szigyarto CA, Odeberg J, Djureinovic D, Takanen JO, Hober S, Alm T, Edqvist PH, Berling H, Tegel H, Mulder J, Rockberg J, Nilsson P, Schwenk JM, Hamsten M, von Feilitzen K, Forsberg M, Persson L, Johansson F, Zwahlen M, von Heijne G, Nielsen J, Pontén F. Proteomics. Tissue-based map of the human proteome. Science. 2015 Jan 23;347(6220):1260419.
[26]. Lin J, Song T, Li C, Mao W. GSK-3β in DNA repair, apoptosis, and resistance of chemotherapy, radiotherapy of cancer. BiochimBiophys Acta Mol Cell Res. 2020 May;1867(5):118659.
[27]. Conceição CJF, Moe E, Ribeiro PA, Raposo M. PARP1: A comprehensive review of its mechanisms, therapeutic implications and emerging cancer treatments. BiochimBiophys Acta Rev Cancer. 2025 Apr;1880(2):189282.
[28]. Ayoubi HA, Mahjoubi F, Mirzaei R. Investigation of the human H3.3B (H3F3B) gene expression as a novel marker in patients with colorectal cancer. J Gastrointest Oncol. 2017 Feb;8(1):64-69.
[29]. Sirover MA. Pleiotropic effects of moonlighting glyceraldehyde-3-phosphate dehydrogenase (GAPDH) in cancer progression, invasiveness, and metastases. Cancer Metastasis Rev. 2018 Dec;37(4):665-676.
[30]. He N, Zhang J, Liu M, Yin L. Elucidating the mechanism of plasticizers inducing breast cancer through network toxicology and molecular docking analysis. Ecotoxicol Environ Saf. 2024 Oct 1;284:116866.
[31]. Westaby D, Jiménez-Vacas JM, Figueiredo I, Rekowski J, Pettinger C, Gurel B, Lundberg A, Bogdan D, Buroni L, Neeb A, Padilha A, Taylor J, Zeng W, Das S, Hobern E, Riisnaes R, Crespo M, Miranda S, Ferreira A, Hanratty BP, Nava Rodrigues D, Bertan C, Seed G, Fenor de La Maza MLD, Guo C, Carmichael J, Grochot R, Chandran K, Stavridi A, Varkaris A, Stylianou N, Hollier BG, Tunariu N, Balk SP, Carreira S, Yuan W, Nelson PS, Corey E, Haffner M, de Bono J, Sharp A. BCL2 expression is enriched in advanced prostate cancer with features of lineage plasticity. J Clin Invest. 2024 Sep 17;134(18):e179998.
[32]. Jiang H, Li H. Prognostic values of tumoral MMP2 and MMP9 overexpression in breast cancer: a systematic review and meta-analysis. BMC Cancer. 2021 Feb 10;21(1):149.
[33]. Sun M, Wang G, Paciga JE, Feldman RI, Yuan ZQ, Ma XL, Shelley SA, Jove R, Tsichlis PN, Nicosia SV, Cheng JQ. AKT1/PKBalpha kinase is frequently elevated in human cancers and its constitutive activation is required for oncogenic transformation in NIH3T3 cells. Am J Pathol. 2001 Aug;159(2):431-7.
[34]. Alwhaibi A, Verma A, Adil MS, Somanath PR. The unconventional role of Akt1 in the advanced cancers and in diabetes-promoted carcinogenesis. Pharmacol Res. 2019 Jul;145:104270.
[35]. Cancer Genome Atlas Network. Comprehensive molecular characterization of human colon and rectal cancer. Nature. 2012 Jul 18;487(7407):330-7.
[36]. GTEx Consortium. Erratum: Genetic effects on gene expression across human tissues. Nature. 2018 Jan 25;553(7689):530.