The Open Bioinformatics Journal

Content list available at: https://openbioinformaticsjournal.com

RESEARCH ARTICLE

Unveiling Crucial Proteins in Zone 2 of the Human Protein Interaction Network: Implications for Cancer Research and Therapeutic Targeting

Emad Fadhal[1,*]

[1]*Department of Mathematics and Statistics, College of Science, King Faisal University, P. O. Box 400, Al-Ahsa 31982, Saudi Arabia*

Abstract:

Background:

Protein-protein interaction networks are of great importance for understanding the complexity of biological processes and diseases, including cancer. However, detecting key proteins that regulate and mediate biological processes within these networks can be challenging due to their enormous size and complexity. Identification of these important proteins is of great importance for identifying therapeutic targets and elucidating molecular mechanisms in various types of cancer.

Aims:

The aim of this study was to investigate the importance of zone 2, the central zone of the protein interaction network in humans, and to identify potential therapeutic targets for common proteins expressed in different types of cancer.

Method:

We analyze zone 2 of the human protein interaction network and identify proteins within the network that function as key regulators or mediators of biological processes. We use multiple biological databases to collect data on protein-protein interactions and cancer types. We analyze the data to obtain promising proteins for different types of cancer.

Results:

Our analysis identified several important proteins in several types of cancer. These proteins play important roles in regulating biological processes within the network.

Conclusion:

Our approach effectively identifies essential proteins within protein-protein interaction networks across multiple cancer types. Furthermore, the identification of key proteins in zone 2 of the human protein interaction network will provide new insights into the molecular mechanisms underlying various cancer types and pave the way for new therapeutic targets.

Keywords: Human-protein interaction networks, Signalling proteins, Central zone, Cancer biology, Drug development, Therapeutic Targeting.

Article History	Received: July 31, 2023	Revised: August 16, 2023	Accepted: August 25, 2023

1. INTRODUCTION

In the field of cancer research, graph theory analysis is an increasingly valuable tool for analyzing protein-protein interaction networks (PPIs) and revealing their structural and functional properties. By mapping proteins as nodes and their interactions as edges, this approach allows us to comprehensively study the topological features of the network and the major players that play important roles in biological processes can be identified. Graph theory analysis has been used in many studies to investigate PPI in various types of cancer such as breast cancer, lung cancer, glioblastoma, and hepatocellular carcinoma [1 - 3]. Graph theory identifies key nodes associated with disease progression and patient survival in breast cancer and reveals key proteins involved in tumor progression, immune response, and drug resistance in hepatocellular carcinoma have been successful [4, 5]. In addition, functionally important common key nodes have been identified in different types of cancer, highlighting their potential as promising targets for broad-spectrum cancer

* Address correspondence to this author at the Department of Mathematics & Statistics, College of Science, King Faisal University, P. O. Box 400, Al-Ahsa 31982, Saudi Arabia; E-mail: efadhal@kfu.edu.sa

therapy [6 - 12].

Our goal in this study is to use tools that have been successful in graph theory analysis to develop human studies that act on multiple cancer types such as breast, prostate, small cell lung, colorectal, non-small cell lung, endometrial, pancreatic, thyroid, and bladder cancer [13 - 15]. This investigation will focus on zone 2, two distances from the center of the network to discover important nodal points associated with different types of cancer.

2. METHODOLOGY

In our previous work, we used specific methods (http://www.boost.org/) to study protein-protein interactions (PPIs). We treated these interactions as a metric space and used graph theory tools for analysis [13]. Our approach involves conceptualizing all PPIs as a metric space, locating a central node within each network, and classifying the remaining proteins into discrete 'zones' based on their graph-theoretic distance from the central protein. For example, proteins in zone 1 were located just one step away from the midpoint, while zone 2 contained proteins two steps away. Our study reveals a radial pattern of protein interactions revolving around a central node. Remarkably, there was a pronounced accumulation of protein in the center of the network, with less protein moving away from this central point. Furthermore, we identified a significant biological significance in the hierarchical distribution of proteins radiating from the center. By systematically and concisely evaluating PPIs as a metric space that emphasizes the relative position of zones with respect to the center, we effectively highlight significant differences between PPI networks in healthy and diseased tissues. We suggested that centrally located proteins, especially those involved in sensory function, may serve as promising targets for therapeutic intervention. Such proteins should be thoroughly evaluated based on our metric space methodology in future studies.

Our ongoing work, which builds on the framework outlined in previous studies, shows that essential proteins are present at high concentrations in central zones within specific human PPI networks and have established drug targets. ing. Moreover, these central zones exhibit a more substantial state, supporting the concept of potential utility in drug target discovery quests [14]. Expanding on the scope of previous analytical efforts, the current study focuses on zone 2. This zone is characterized by an enriched binding hub for proteins associated with a variety of cellular functions, including signaling pathways, immune responses, blood clotting mechanisms, and disease associations.

3. PATHWAY ASSESSMENT AND FUNCTIONAL ENRICHMENT INTERPRETATION

To determine the biological importance of zone 2 within the PPI network, we performed protein overexpression pathway analysis to identify specific functions that could be attributed to zone 2. A number of web services were used to perform zone 2 enrichment analysis, including gene set enrichment in comparative toxicogenomics databases and gene ontology term enrichment analysis. Statistical significance was set at a threshold of 0.01. Finally, to explore the possible functional specialization of zone 2, we calculated the ratio of proteins involved in each enriched signaling pathway.

3.1. Analysis of Protein Pathways Associated with Oncogenes and Tumor Suppressors

A thorough analysis of protein scores was performed with particular emphasis on scores associated with oncogenes and tumor suppressors. Using data from large-scale cancer genome sequencing studies, signaling pathways exhibiting enrichment were identified. In particular, our analysis focused on investigating interactions that yielded significant results. Results showed that these interactions often involve genes causally associated with cancer [16].

3.2. Proteins Essential for Cellular Processes, Signalling, Growth, Cell Cycle Regulation, and Potential Therapeutic Targets

To assess zone 2 of the human functional protein interaction network [17]. We identified a panel of noteworthy human proteins by taking advantage of the corresponding gene knockout phenotypes observed in mice [18].

4. RESULTS

In our previous work, we found that interactions between human proteins can be modeled as a metric space [13]. This involves grouping proteins into different zones based on their proximity to hub proteins that are tightly bound and essential to biological networks.

Recently, a zone near the network center was shown to contain important proteins and potential therapeutic targets [19]. In particular, we showed that zone 2 contains proteins specialized for specific household functions. For example, oncogenes such as PIK3CA, EGFR, AKT1, MAP2K1, AR, JAK2, and JAK1 are involved in various cellular processes and signaling pathways involved in cell growth, proliferation, survival, metabolism, and signaling. Furthermore, we found that suppressor proteins such as EP300, TP53, CASP8, PIK3R1, CREBBP, and PTCH1 are of interest in gene regulation, DNA repair, apoptosis, and cell signaling [20]. Recent studies have shown that key zone 2 proteins such as KIT, ERBB2, PDGFRA, MET, FGFR2, and FGFR3 are involved in numerous cancer-associated signaling pathways, particularly the PI3K/AKT pathway [21].

On this basis, our current study aims to examine zone 2, the most highly interconnected zone rich in proteins involved in signal transduction, immune response, hemostasis, and disease pathways. This zone contains proteins involved in various cellular functions such as cell cycle regulation and response to DNA damage [22]. To determine whether specific signaling pathways were enriched in this zone, we mapped them to proteins in the KEGG signaling pathway [23]. Our investigation focused on 4497 proteins in zone 2, which are diverse in breast, prostate, small cell lung, colorectal, non-small cell lung, endometrial, pancreatic, thyroid and bladder cancers. We aimed to identify its involvement in various cancer pathways (Table **1**).

Table 1. Distribution of cancer-related proteins within zone 2.

Type of Cancer	Number of Proteins
Breast	101
Prostate	52
Small cell lung	52
Colorectal	38
Non-small cell lung	34
Endometrial	32
Pancreatic	29
Thyroid	19
Bladder cancer	19

4.1. Distribution of Essential, Signalling, Growth, Cell Cycle, MAPK Cascde, Positive Signalling and Negative Signalling in Cancer-related Proteins within Zone 2

Activation and regulation of signaling pathways play an important role in cancer development and progression. Cancer cells often alter and disrupt the signaling pathways that enable proliferation and survival, so it is important to focus on cancer therapies that target these signaling pathways. Focusing on these signaling pathways can disrupt their function, ultimately affecting cancer cell proliferation and viability [24 - 27]. Table **2** shows that signaling proteins account for the major proportion of all cancers at 85.63%, followed by essential proteins at 53.98%. Here are the ratios for the rest of the functions: positive signal (35.37%), MAPK cascade (35.10%), negative signal (17.02%), cell cycle (15.15%), and proliferation (8.77%).

4.2. Distribution of Apoptosis, Positive Apoptosis, Negative Apoptosis, Oncogenes Tumor Suppressor, and Therapeutic Target in Cancer-related Proteins within Zone 2

Cancer networks rely heavily on proteins that promote or prevent cancer, such as oncogenes and tumor suppressor genes, respectively. Interactions between these proteins have profound effects on cancer cell behavior [28, 29]. Our findings show that oncogenes accounted for the largest proportion at 11.7%, suggesting that these proteins may be promising targets for drug development. Residual functions such as tumor suppressors, successful therapeutic targets, proteins, and apoptosis have low percentages of 0.26% to 6.11%, suggesting that they may also be involved in cancer, albeit to a lesser extent (Table **3**).

4.3. Common Proteins Among Types of Cancer Pathways and their Function

Since cancer does not arise from a single gene or protein, identifying proteins shared within cancer networks is of great importance. Rather, it is the result of a complex labyrinth of interactions between various genes and proteins that monitor cell growth, regeneration, and death. Therefore, in our study, we identified two proteins, BRAF and KRAS, which are present in all cancers except small-cell lung cancer, for study. These proteins play important roles as MAPKs, positive signaling, and oncogenic proteins.

Table 2. Distribution of essential, signalling, growth, cell cycle, MAPK cascde, positive signalling and negative signalling in cancer-related proteins within zone 2.

Cancer Type	# of Proteins	E	S	G	C	M	P/S	N/S
Breast	101	51 (50.49%)	99 (98%)	10 (9.90%)	11 (10.89%)	37 (36.63%)	45 (44.45%)	23 (22.77%)
Prostate	52	31 (59.61%)	41 (78.74%)	4 (7.69%)	13 (25%)	21 (40.38%)	20 (38.46%)	10 (19.23%)
Small cell lung	52	27 (51.92%)	28 (53.84%)	1 (1.92%)	6 (11.53%)	5 (9.61%)	8 (15.38%)	3 (5.76%)
Colorectal	38	22 (57.89%)	35 (92.10%)	5 (13.15%)	3 (7.89%)	11 (28.9%)	11 (28.9%)	7 (14.42%)
Non-small cell lung	34	15 (44.11%)	32 (94.11%)	1 (2.94%)	8 (23.52%)	11 (32.35%)	10 (29.41%)	4 (11.76%)
Endometrial	32	21 (65.62%)	30 (93.75%)	3 (9.37%)	4 (12.5%)	12 (37.5%)	12 (37.5%)	10 (31.25%)
Pancreatic	29	15 (51.72%)	26 (89.65%)	4 (13.79%)	5 (17.24%)	11 (37.93%)	9 (31.03%)	1 (3.44%)
Thyroid	19	11 (57.8%)	17 (89.4%)	2 (10.52%)	2 (10.52%)	6 (31.5%)	8 (42.10%)	4 (21.05%)
Bladder cancer	19	10 (52.63%)	14 (73.68%)	3 (15.78%)	5 (26.31%)	8 (42.10%)	10 (52.63%)	2 (10.52%)

Abbreviations: E= Essential, S= Signalling, G= Growth, C= Cell cycle, M= MAPK cascde, P/S= Positive signalling, N/S= Negative signalling.

Table 3. Distribution of apoptosis, positive apoptosis, negative apoptosis, oncogenes tumor suppressor, and therapeutic target in cancer-related proteins within zone 2.

Cancer Type	#of Proteins	A	P/A	N/A	O	SG	T
Breast	101	0 (0.00%)	0 (0.00%)	0 (0.00%)	7 (6.93%)	5 (4.95%)	5 (4.95%)
Prostate	52	0 (0.00%)	0 (0.00%)	0 (0.00%)	8 (15.38%)	1 (1.92%)	4 (7.69%)
Small cell lung	52	1 (1.92%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.92%)	3 (5.76%)
Colorectal	38	1 (2.63%)	1 (2.63%)	0 (0.00%)	3 (7.89%)	7 (18.42%)	2 (5.26%)
Non-small cell lung	34	0 (0.00%)	0 (0.00%)	0 (0.00%)	6 (17.64%)	0 (0.00%)	3 (8.82%)
Endometrial	32	0 (0.00%)	0 (0.00%)	0 (0.00%)	6 (18.75%)	5 (15.6%)	1 (3.12%)
Pancreatic	29	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (10.34%)	2 (6.89%)	1 (3.44%)
Thyroid	19	0 (0.00%)	0 (0.00%)	0 (0.00%)	5 (26.31%)	1 (5.26%)	3 (15.78%)

(Table 3) contd.....

Cancer Type	#of Proteins	A	P/A	N/A	O	SG	T
Bladder cancer	19	0 (0.00%)	0 (0.00%)	0 (0.00%)	6 (31.57%)	1 (5.26%)	1 (5.26%)

Abbreviations: A= Apoptosis, P/A= Positive apoptosis, N/A= Negative apoptosis, O = Oncogenes, SG= Suppressor gene, T= Target protein.

Table **4** shows the overlapping distribution of proteins in various cancers, including endometrial, small cell lung, breast, and prostate cancers, all of which are signaling proteins. Among them, PTEN is a negative signaling protein and a tumor suppressor that regulates the cell cycle. In addition, the PTEN gene contains coding sequences for enzymes present in almost all types of body tissue. This enzyme acts as a tumor suppressor by inhibiting and thereby regulating excessive and uncontrolled cell proliferation during cell division [30].

Table 4. Distribution of essential, signalling, cell cycle, positive signalling, negative signalling and tumor suppressor in cancer-related proteins within zone 2.

Cancer Type	Common Proteins	E	S	C	P/S	N/S	SG
Endometrial Small cell lung Breast Prostate	PTEN	✓	✓	✓	×	✓	✓
	PIK3CD	-	✓	×	×	×	×
	PIK3CB	✓	✓	×	×	×	×
	AKT2	✓	✓	×	✓	×	×
	AKT3	✓	✓	×	×	×	×
	PIK3R3	×	✓	×	×	×	×
	PIK3R2	×	✓	×	×	×	×

Abbreviations: E = Essential, S = Signalling, C = Cell cycle, N/S = Negative signalling, P/S = Positive signalling, SG = Suppressor gene.

Table **5** shows proteins commonly present in breast, prostate, colorectal, non-small cell lung, endometrial, pancreatic, and bladder cancers. This observation indicates that these proteins are part of signaling pathways that regulate various important functions of the cell and that they all function as oncogenes.

Table 5. Distribution of essential, signalling, MAPK cascde, positive signalling and oncogenes in cancer-related proteins within zone 2.

Cancer type	Common Proteins	E	S	M	P/S	O
Breast Prostate Colorectal Non small cell lung Endomentrial Pancreatic bladder	ARAF	×	✓	✓	✓	✓
	BRAF	✓	✓	✓	✓	✓
	KRAS	✓	✓	✓	✓	✓

Abbreviations: E = Essential, S = Signalling, M = MAPK cascade, P/S = Positive signalling O = Oncogenes.

Finally, Table **6** lists proteins commonly present in the breast, prostate, colorectal, non-small cell lung, endometrial, pancreatic, and small cell lung cancer. This observation indicates that all these proteins are involved in signaling pathways. In general, the PIK3CA, PIK3CB, and AKT2 genes are important for various cellular processes. Mutations in these genes are associated with several diseases such as cancer and diabetes [31, 32].

5. DISCUSSION

In this study, we examine the importance of zone 2, the central zone of the human protein interaction network. Our goal was to identify common proteins expressed in different cancer types to target therapeutics. The results demonstrate the predominance of signaling and essential proteins in all cancers highlighted in Table **2**. Oncogenes and tumor suppressor genes have also been discussed, suggesting that a greater proportion of oncogenes are promising targets for drug development. Table 3 provides further details on protein function in cancer. Our results showed that there are several proteins that are consistently expressed in most cancers. These include BRAF and KRAS, which play key roles in the intracellular signaling pathway known as the MAPK/ERK pathway. This pathway helps regulate cell growth, cell division, and differentiation. Both proteins are important targets for cancer therapy, and drugs targeting these proteins are currently being developed and tested in clinical trials. In addition, Tables **4**, **5**, and **6** list proteins found in various types of cancer and their roles in regulating cell growth, cell regeneration, and cell proliferation. Furthermore, the presence of PTEN has also been observed in endometrial cancer, small-cell lung cancer, breast cancer, and prostate cancer. It has been identified as a negative signaling protein and tumor suppressor that regulates the cell cycle and helps prevent uncontrolled cell proliferation. In addition, the proteins PIK3CA, PIK3CB, and AKT2 are involved in a variety of cellular processes and mutations have been implicated in cancer and diabetes.

Table 6. Distribution of essential, signalling, positive signalling and MAPK cascade, in cancer-related proteins within zone 2.

Cancer type	Common Proteins	E	S	P/S	M
Breast Prostate Colorectal Non small cell lung Endomentrial Pancreatic Small cell lung	PIK3CB	×	✓	×	×
	PIK3CD	✓	✓	×	✓
	PIK3R3	×	✓	×	×
	PIK3R2	×	✓	×	×
	AKT2	✓	✓	✓	✓
	AKT3	✓	✓	×	×

Abbreviations: E = Essential, S = Signalling, M = MAPK cascade, P/S = Positive signalling.

CONCLUSION

This study focuses on investigating the importance of zone 2, the central zone of the human protein interaction network, with the aim of identifying common proteins expressed in different cancers. Our results show that the predominance of signaling and essential proteins in all cancers presents promising targets for drug development. Consistent expression of proteins such as BRAF and KRAS in most cancers underlines their importance in regulating cell proliferation, cell division, and differentiation *via* the MAPK/ERK pathway. The identification of tumor suppressor genes such as PTEN and their various roles in regulating the cell cycle and preventing uncontrolled cell proliferation provides potential targets for cancer therapy. In addition, proteins PIK3CA, PIK3CB, and AKT2, which are involved in various cellular processes, are associated with cancer and diabetes when mutated. These

findings reveal the importance of specific proteins in cancer progression and provide potential avenues for targeted therapy. Further research and clinical studies are needed to explore the therapeutic potential of these proteins in terms of cancer therapy.

ETHICAL STATEMENT

No animals were used in this research. Our research work does not involve human participants or patient material. The study primarily relies on data from established databases and does not directly involve any interaction, intervention, or collection of information from individuals. It is purely a research article based on existing data sources, with no direct involvement of human subjects.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

All the data and supporting information are provided within the article.

FUNDING

This research was funded by the Deanship of Scientific Research, Vice Presidency for Graduate Studies and Scientific Research, King Faisal University, Saudi Arabia [Grant No. 3948].

CONFLICT OF INTEREST

The author declares that they have no competing interests.

ACKNOWLEDGEMENTS

: The author would like to thank Scientific Research, Vice Presidency for Graduate Studies and Scientific Research, King Faisal University, Saudi Arabia for support.

REFERENCES

[1] Zhang Y, Xiang J, Tang L, *et al.* Identifying breast cancer-related genes based on a novel computational framework involving KEGG pathways and PPI network modularity. Front Genet 2021; 12: 596794. [http://dx.doi.org/10.3389/fgene.2021.596794] [PMID: 34484285]

[2] Shi K, Li N, Yang M, Li W. Identification of key genes and pathways in female lung cancer patients who never smoked by a bioinformatics analysis. J Cancer 2019; 10(1): 51-60. [http://dx.doi.org/10.7150/jca.26908] [PMID: 30662525]

[3] Chen H, Cai H, Xu X, *et al.* Identification of key genes and pathways in glioblastoma by bioinformatics analysis. Int J Mol Med 2019; 43(2): 809-18. [http://dx.doi.org/10.3892/ijmm.2018.3996]

[4] Fang E, Zhang X. Identification of breast cancer hub genes and analysis of prognostic values using integrated bioinformatics analysis. Cancer Biomark 2017; 21(1): 373-81. [PMID: 29081411]

[5] Zhang C, Han Y, Li X, Zhang J. Analysis of hub genes and pathways in hepatocellular carcinoma by bioinformatics analysis. BioMed Res Int 2020; 8814179.

[6] Safari-Alighiarloo N, Taghizadeh M, Rezaei-Tavirani M, Goliaei B, Peyvandi AA. Protein-protein interaction networks (PPI) and complex diseases. Gastroenterol Hepatol Bed Bench 2014; 7(1): 17-31. [PMID: 25436094]

[7] Zhang X, Wang Y. Identification of hub genes and key pathways associated with the progression of gynecological cancer. Oncol Lett 2019; 18(6): 6516-24. [http://dx.doi.org/10.3892/ol.2019.11004] [PMID: 31788113]

[8] Hermawan A, Ikawati M, Jenie RI, *et al.* Identification of potential therapeutic target of naringenin in breast cancer stem cells inhibition by bioinformatics and *in vitro* studies. Saudi Pharm J 2021; 29(1): 12-26. [http://dx.doi.org/10.1016/j.jsps.2020.12.002] [PMID: 33603536]

[9] Song Y, DiMaio F, Wang RY, Kim D. GraphProt: Modeling binding preferences of RNA-binding proteins. Genome Biol 2017; 18(1): 220. [http://dx.doi.org/10.1186/s13059-017-1349-2] [PMID: 29141660]

[10] Li C, Li X, Miao Y, Wang Q, Jiang W. Identification of hub genes and key pathways associated with progression of breast cancer based on weighted gene co-expression network analysis. Front Genet 2019; 10: 380. [http://dx.doi.org/10.3389/fgene.2019.00380]

[11] Cohen AS, Grudzinski J, Smith GT, *et al.* First-in-human pet imaging and estimated radiation dosimetry of l-[5-11C]-glutamine in patients with metastatic colorectal cancer. J Nucl Med 2022; 63(1): 36-43. [http://dx.doi.org/10.2967/jnumed.120.261594] [PMID: 33931465]

[12] Kasikci Y, Gronemeyer H. Complexity against current cancer research: Are we on the wrong track? Int J Cancer 2022; 150(10): 1569-78. [http://dx.doi.org/10.1002/ijc.33912] [PMID: 34921726]

[13] Fadhal E, Gamieldien J, Mwambene EC. Protein interaction networks as metric spaces: A novel perspective on distribution of hubs. BMC Syst Biol 2014; 8(1): 6. [http://dx.doi.org/10.1186/1752-0509-8-6] [PMID: 24438364]

[14] Fadhal E, Mwambene EC, Gamieldien J. Modelling human protein interaction networks as metric spaces has potential in disease research and drug target discovery. BMC Syst Biol 2014; 8(1): 68. [http://dx.doi.org/10.1186/1752-0509-8-68] [PMID: 24929653]

[15] Fadhal E, Gamieldien J, Mwambene EC. Self-similarity of human protein interaction networks: A novel strategy of distinguishing proteins. Sci Rep 2015; 5(1): 7628. [http://dx.doi.org/10.1038/srep07628] [PMID: 25720740]

[16] Vogelstein B, Papadopoulos N, Velculescu VE, Zhou S, Diaz LA Jr, Kinzler KW. Cancer genome landscapes. science 2013; 339(6127): 1546-58.

[17] Wu G, Feng X, Stein L. A human functional protein interaction network and its application to cancer data analysis. Genome Biol 2010; 11(5): R53. [http://dx.doi.org/10.1186/gb-2010-11-5-r53] [PMID: 20482850]

[18] Bult CJ, Eppig JT, Blake JA, Kadin JA, Richardson JE. The mouse genome database: Genotypes, phenotypes, and models of human disease. Nucleic Acids Res 2013; 41(D1): D885-91. [http://dx.doi.org/10.1093/nar/gks1115] [PMID: 23175610]

[19] Fadhal E. Exploring the significance of zone 1 in human protein interaction networks: Identifying potential therapeutic targets for cancer treatment. Oncology and Radiotherapy 2023; 17(8): 249-53.

[20] Fadhal E. Unraveling the significance of signal transduction pathways: Key players in cancer development and progression. J Cancer Ther Res 2023; 3(1): 1-9.

[21] Fadhal E. A comprehensive analysis of the PI3K/AKT pathway: Unveiling key proteins and therapeutic targets for cancer treatment. Cancer Inform 2023; 22: 11769351231194273. [http://dx.doi.org/10.1177/11769351231194273]

[22] Kanehisa M, Goto S, Furumichi M, Tanabe M, Hirakawa M. KEGG for representation and analysis of molecular networks involving diseases and drugs. Nucleic Acids Res 2010; 38(Database issue)(1): D355-60. [http://dx.doi.org/10.1093/nar/gkp896] [PMID: 19880382]

[23] Kanehisa M. The KEGG database.In *'In silico'* simulation of biological processes.Novartis Foundation Symposium. Chichester, UK: John Wiley & Sons, Ltd 2002; 247: pp. 91-103. [http://dx.doi.org/10.1002/0470857897.ch8]

[24] Yang Y, Li X, Wang T, Guo Q, Xi T, Zheng L. Emerging agents that target signaling pathways in cancer stem cells. J Hematol Oncol 2020; 13(1): 60. [http://dx.doi.org/10.1186/s13045-020-00901-6] [PMID: 32456660]

[25] Nouri Z, Fakhri S, Nouri K, Wallace CE, Farzaei MH, Bishayee A. Targeting multiple signaling pathways in cancer: The rutin therapeutic approach. Cancers 2020; 12(8): 2276. [http://dx.doi.org/10.3390/cancers12082276] [PMID: 32823876]

[26] Clara JA, Monge C, Yang Y, Takebe N. Targeting signalling pathways and the immune microenvironment of cancer stem cells : A clinical update. Nat Rev Clin Oncol 2020; 17(4): 204-32. [http://dx.doi.org/10.1038/s41571-019-0293-2] [PMID: 31792354]

[27] He Y, Xu W, Xiao YT, Huang H, Gu D, Ren S. Targeting signaling

pathways in prostate cancer: Mechanisms and clinical trials. Signal Transduct Target Ther 2022; 7(1): 198.
[http://dx.doi.org/10.1038/s41392-022-01042-7] [PMID: 35750683]

[28] Levine AJ, Puzio-Kuter AM. The control of the metabolic switch in cancers by oncogenes and tumor suppressor genes. Science 2010; 330(6009): 1340-4.
[http://dx.doi.org/10.1126/science.1193494] [PMID: 21127244]

[29] Aunoble B, Sanches R, Didier E, Bignon YJ. Major oncogenes and tumor suppressor genes involved in epithelial ovarian cancer (review). Int J Oncol 2000; 16(3): 567-76.
[http://dx.doi.org/10.3892/ijo.16.3.567] [PMID: 10675491]

[30] Muthumanickam S, Indhumathi T, Boomi P, *et al. In silico* approach of naringin as potent phosphatase and tensin homolog (PTEN) protein agonist against prostate cancer. J Biomol Struct Dyn 2022; 40(4): 1629-38.
[http://dx.doi.org/10.1080/07391102.2020.1830855] [PMID: 33034258]

[31] Canaud G, Bienaimé F, Viau A, *et al.* AKT2 is essential to maintain podocyte viability and function during chronic kidney disease. Nat Med 2013; 19(10): 1288-96.
[http://dx.doi.org/10.1038/nm.3313] [PMID: 24056770]

[32] Crowder RJ, Phommaly C, Tao Y, *et al.* PIK3CA and PIK3CB inhibition produce synthetic lethality when combined with estrogen deprivation in estrogen receptor-positive breast cancer. Cancer Res 2009; 69(9): 3955-62.
[http://dx.doi.org/10.1158/0008-5472.CAN-08-4450] [PMID: 19366795]