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In silico analysis identifying overlapped genes between diabetes and breast cancer, targeting candidates via doxazosin mesylate, a comprehensive analysis

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Abstract

Breast cancer and diabetes share common molecular interactions, mainly through the activation of the breast cancer signaling pathway, namely PI3K/AKT/mTOR and insulin signaling. These common signaling associations can reveal a dysfunction in the metabolic order that can influence breast cancer growth and lead to becoming more aggressive and metastasis. In this in-silico research, the potential of Doxazosin Mesylate to target crosstalk signaling diseases, namely breast cancer and diabetes. Doxazosin mesylate has a significant in-vitro analysis by exhibiting the cell viability of breast cancer cell line, a comprehensive in-silico analysis is performed to support the importance of targeting diabetes-related proteins using GNINA AI-based molecular docking tool. This study aims to identify whether the insulin signaling candidates need to be emphasized in the therapeutic target approach of breast cancer or not. The bioinformatic analysis revealed a strong binding affinity of IRS2 with Doxazosin Mesylate, suggesting a potential therapeutic target that can enhance the treatment outcomes by interfering with treatment resistance and responses. The studies' findings illustrated that, meanwhile, Doxazosin Mesylate acts primarily on the oncogenes; they have other interactions with the insulin protein pathway. This supports that it should be taken as a biological consideration and a secondary target candidate for breast cancer.

Keywords: Diabetes, breast cancer, molecular docking, overlapped genes, and Doxazosin Mesylate

1. Introduction

The increase in obesity and type 2 diabetes has revealed an overlap between signaling pathways of metabolic activities and cancer disorders. Statistical analysis in the U.S. states that over 100 million people with T2D have a higher risk of developing solid tumors, including breast cancer, colorectal cancer, and endometrial cancer [1]. Interestingly, they tend to create more aggressive phenotypes of different tumors, which leads to a reduction in survival rates. This could be due to various cellular functions that influence the weakness or strength of cancer tumors, particularly breast cancer. On a molecular level, it highlights a variety of interconnected signaling

pathways and metabolic processes, with a focus on the breast cancer pathway, specifically the PI3K/AKT/mTOR signaling pathway.

The interference between these pathways, hyperinsulinemia, and chronic hyperglycemia can support and mimic a tumor microenvironment to grow and develop, and to be more metastatic [1], [2].

Shedding light on breast cancer, which is one of the most common threatening tumors in women globally. It's associated with a higher morbidity and mortality rate. This constantly develops the activation of different pathways, specifically the PAM pathway. The PI3K/AKT/mTOR signaling pathway mediates cell proliferation, survival, and apoptosis inhibition. This is an ideal mechanism for tumor growth. Recent therapeutic strategies using a targeting approach direct their view on these pathways. Although there are some limitations and their side effects are still being studied, recent studies reveal that using a repurposed drug approach is a potential way to increase the efficacy of breast cancer therapy [3].

In addition, emerging studies reveal the connection between diabetes and cancer genes that share an association with the breast cancer pathways. They are considered a metabolic disorder that leads to insulin resistance. The central components that affect the glucose level in the body include IRS, IGF, and PPARG [4]. These genes tend to be modulated and targeted using different anti-diabetic drugs such as metformin and pioglitazone [5]. Studying the overlap between anticancer and diabetes molecular target interactions is becoming common nowadays. The use of drug repurposing provides evidence to investigate whether Doxazosin Mesylate [6], which is approved by the FDA and used to treat hypertension, can share effective results in both diseases. It becomes a popular ligand against breast cancer signaling pathways [7]. However, what is its potential interaction against the diabetes related genes that influence the metastasis of cancer cells? This remains unexplored.

This study will illustrate a better understanding of whether Doxazosin Mesylate is connected to metabolic pathways, and whether targeting crosstalk pathways or genes can influence the future therapeutic strategy of cancer [8].

2. Research method

2.1 Selection of targeted genes

Looking for target genes that are associated with breast cancer and diabetes were identified based on a literature review and the application of bioinformatic analysis. For further validation of the correlation between the selected proteins that are associated with breast cancer and diabetes, a protein-protein interaction analysis was conducted on the seven selected proteins using the STRING bioinformatics tool, which explores the protein-protein interaction network, providing an extensive list of genes and proteins [9]. This platform provides rapid visualization of the interaction network, providing access to gene and protein relationships. Regarding gene annotation, it was retrieved via the NCBI and Uniprot databases, where we found a detailed description of domains, 3D structures, and gene sequences of the study candidates [10], [11].

2.2 Drug retrieval

Doxazosin Mesylate, a repurposed drug, was selected for this study, and its structure was represented using a customized Simplified Molecular Input Line Entry System (SMILES) notation for use in computational analyses, which was retrieved from the ChEMBL database [12]. The SMILE was assessed based on pharmacokinetic properties. It's known to be examined for breast cancer. This drug is selected for performing molecular docking to assess the potential interactions between both breast cancer and diabetes associated genes.

2.3 Protein structure preparation

The 3D structures of the selected proteins were retrieved from Universal Protein Resource (Uniprot), a large-scale database consisting of protein and gene information and sequences associated with certain functional

properties, by providing detailed information on their annotations, structure, protein name, and their biological role [13].

2.4 Molecular docking

Performing the interaction between the ligand (Doxazosin Mesylate) and targeted candidates was conducted using the AI-based docking software GNINA. It integrates convolutional neural networks (CNNs), which display a score function that represents the accuracy of ligand binding, and enhances the prediction scores. Thus, it supports the virtual screening and the workflow of drug discovery. The GNINA online server is accessible for Neurosnap users [14].

2.5 Visualization of interaction

Following the molecular docking, the next step was to observe the interacting residues with the ligand, which was achieved using BIOVIA Discovery Studio Visualizer. The software models the molecular docking results by visualizing, analyzing, and preparing the docking complexes between the ligand and the protein [15]. This interpretation can illustrate the stability of the binding affinity between the proteins and the ligand.

3. Results and discussion

3.1 Protein identification using STRING

The STRING map indicates the possible association between the diabetes genes that were selected (Table 1) with the breast cancer PAM pathway, which tells us about the possible interaction between Doxazosin Mesylate and the targeted ligand. It shows that the interactions of proteins involved in the cancer pathway interfere with diabetes genes as well. This illustrates that the biology of both diseases overlaps. Pinpointing the IGF and the insulin genes.

Table 1. Diabetic-cancer overlapping targeted genes

Gene	ID	PDB
IRS1	P35568	7PPM
IRS2	Q9Y4H2	3FQW
IGF1R	P08069	1JQH
PRKCE	Q02156	2WH0
GPR83	Q9NYM4	AF-Q9NYM4-F1
IRS4	O14654	AF-O14654-F1
INSR	P06213	1GAG

Table 1 shows that seven selected genes were chosen based on the significant implication between breast cancer pathways and insulin signaling. The IRS1, IRS2, INSR, and IGF1R genes are responsible for cell proliferation, the increase of glucose uptake, which supports the solidity of breast cancer tumors to be more aggressive, resistance to chemotherapy, and apoptosis inhibition. These characteristics of genes provide insight into regulating and enhancing the therapeutic strategy of cancer, where not just targeting the major pathways, but also shedding light on other proteins, specifically genes that regulate tumor growth [16]. Since it's one of the factors that enhances the tumor microenvironment. Certain genes that overlap with the breast cancer pathway mimic metastasis behavior, which gives the ability for breast cancer to grow uncontrollably. This makes it a promising therapeutic target for breast cancer treatment.

Figure 1 shows that the IRS1 is the central hub in the P-P network. which clearly connected the insulin signaling genes with the PI3K/AKT/mTOR breast cancer signaling pathway. Yet, there is no conclusion on whether these genes are considered the major driver of breast cancer, but they can be an effective factor in breast cancer activation. Usually, when insulin levels are high, breast cancer cells tend to overactivate insulin signaling proteins, which are responsible for cell metabolism, growth, and survival [17]. The network analysis supports this evidence, where it shows the association between different diabetic genes, including INSR, IGF1R, IRS1, IRS2, IRS4, GPR83, and PRKCE. Nevertheless, these modulating genes, such as IGFBP2, have a significant expression level in TNBC. This clearly illustrates how cancer cell growth is connected to insulin pathways

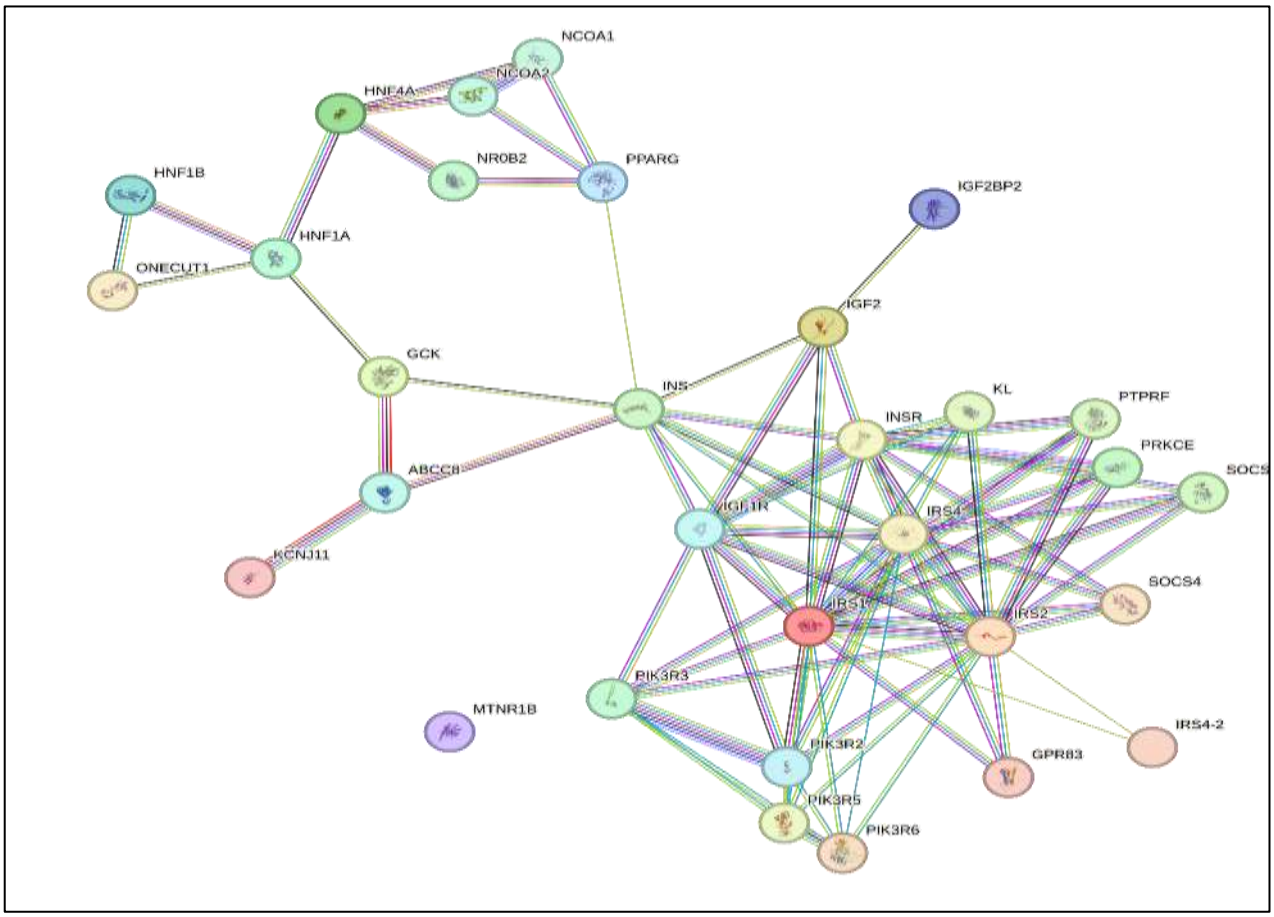

Figure 1. STRING network map of the associated diabetic genes

3.2 Binding Affinity Results via AI-based software GNINA

The docking results shown in Table 2 demonstrated the different interaction strengths among the targeted candidates, that is, diabetic cancer-related genes. Among all proteins, IRS2 ranks the strongest binding affinity compared to other related genes with a score of -8.59 kcal/mol. Followed by PRKCE gene with a score of -8.05 kcal/mol and IGF1R with a score of -7.88 kcal/mol. These affinities are supported by the CNN as evidence for strong interaction. This demonstrates that IRS2 can interfere with cancer treatment response and play a major role in breast cancer pathway activation. These candidates illustrate good and favorable energetic binding, which could support further therapeutic investigation. In addition, INSR and GPR83 also have a moderate binding affinity, compared to IRS2. However, the CNN pose tells us that predicting binding orientation is concerning and doesn't align with the binding affinity score. In contrast to GPR83, while it has slightly lower binding affinity with -7.22 kcal/mol, its CNN pose shows the highest score, suggesting very clear and realistic binding poses obtained. The other proteins, namely IRS4 and IRS1 their binding affinity is very weak, suggesting a weak interaction between the candidates and the ligand – Doxazosin Mesylate.

3.3 Visualized interactions between the ligand and the surrounding residues

The molecular docking and binding affinity results indicate a good fit of the ligand in the binding pocket, identifying several amino acid residues as key interactors. These residues are visualized using the Discovery Studio Visualizer, and 3D and 2D diagrams were prepared for the highest binding affinity scores, which are IRS2, PRKCE, IGF1R, and GPR83.

The 3D interaction diagrams of Doxazosin Mesylate candidates' binding residues obtained from the GNINA tool and visualized using BIOVIA Discovery Studio highlight multiple interacting residues.
The 3D visualization of the Doxazosin Mesylate with IRS2 proteins. Figure 2 illustrates the interacting residues. Approximately 27 residues are recorded with different positions, which is clearly shown in the 3D structure. The receptor surface shows a different charge pattern. The blue color displays the positive electrostatic charge, where certain amino acids are characterized, mainly LYS, ARG, and HIS. The red color represents the negative electrostatic charge, where Asp and GLU are more concentrated in the negative charge localized.

Table 2. Binding affinity of the seven targeted candidates by Doxazosin Mesylate

Parameters	IRS1	IRS2	IGF1R	PRKCE	GPR83	IRS4	INSR
Model	3	1	4	7	1	6	9
Affinity	-6.97	-8.59	-7.88	-8.05	-7.22	-5.69	-7.35
intramolecular energy	0.08	-0.54	-0.52	0.14	-0.58	-0.07	0.06
CNN pose	0.2605	0.34	0.3073	0.2735	0.7243	0.2896	0.1085
CNN affinity	4.302	6.04	4.944	4.533	5.566	4.647	4.854

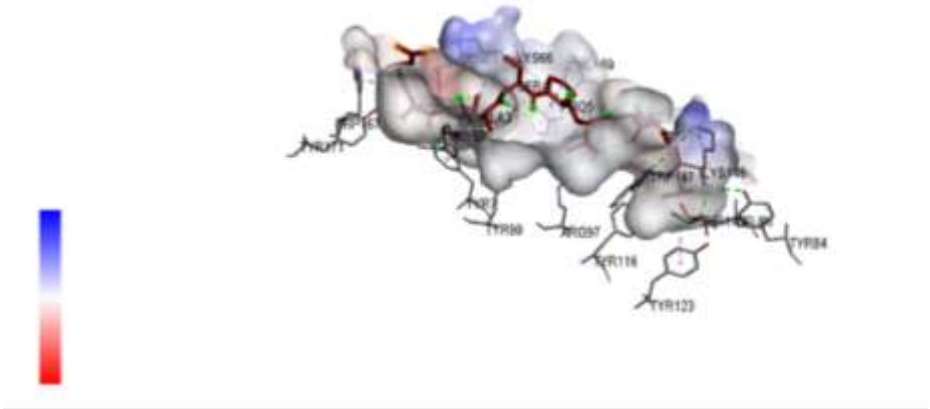

Figure 2. 3D diagram of IRS2 proteins

The PRKCE protein had six interacting residues involved in different interactions, as seen in Figure 3, namely GLU:87, involved in a carbon-carbon-hydrogen bond. ALA:134 and LEU:129 are involved in a conventional hydrogen bond. ALA: 133 is involved in Pi-alkyl interaction. ARG:91 is involved in Pi-cation, and LYS:103 is involved in Pi-sigma. Notably, the relation between the binding affinities and the number of interacting residues doesn’t correlate. Although the IRS2 had a strong binding affinity, it had a huge number of interacting residues,

which could be due to the association between the ligand size and the receptor. While PRKCE had a slight near-binding affinity, it shows only six interacting residues. The negative and positive charges notably form at the edge of the ligand with the interacting residues of the PRKCE protein. However, the hydrophobic part occupies the most, where the charge is neutralized.

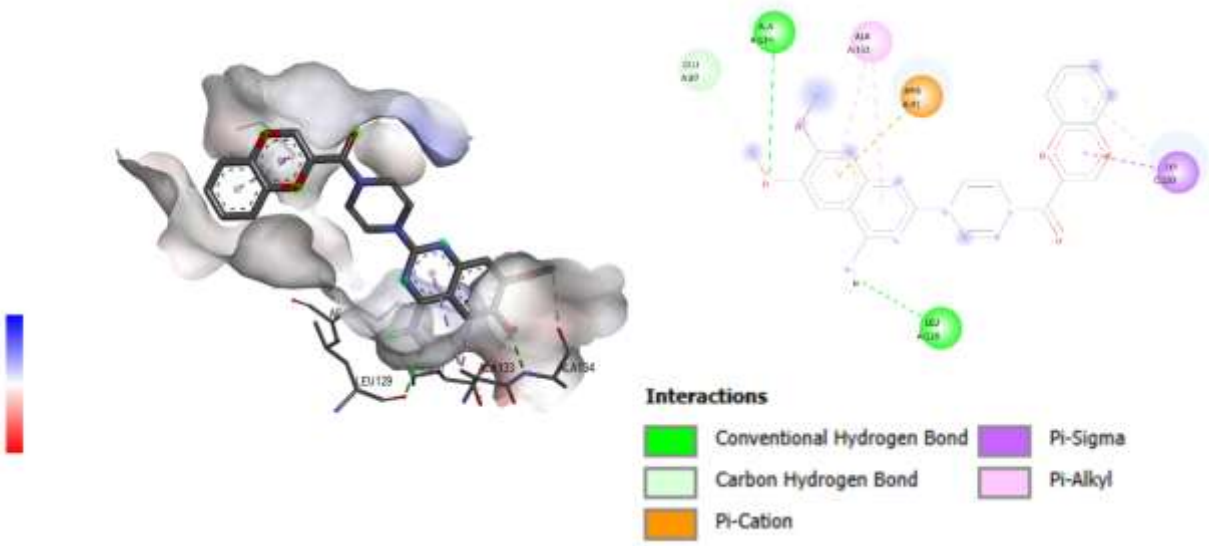

Figure 3. PRKCE interacted with Doxazosin Mesylate

The IGF1R has 4 interacting residues, seen on Figure 4, namely ALA:984 involved in pi-cation interaction, LYS:1055 and TRP:992 involved in Pi-alkyl interaction, ASP:990 involved in conventional hydrogen bond. The negative charge is slightly spread all around the receptor surface.

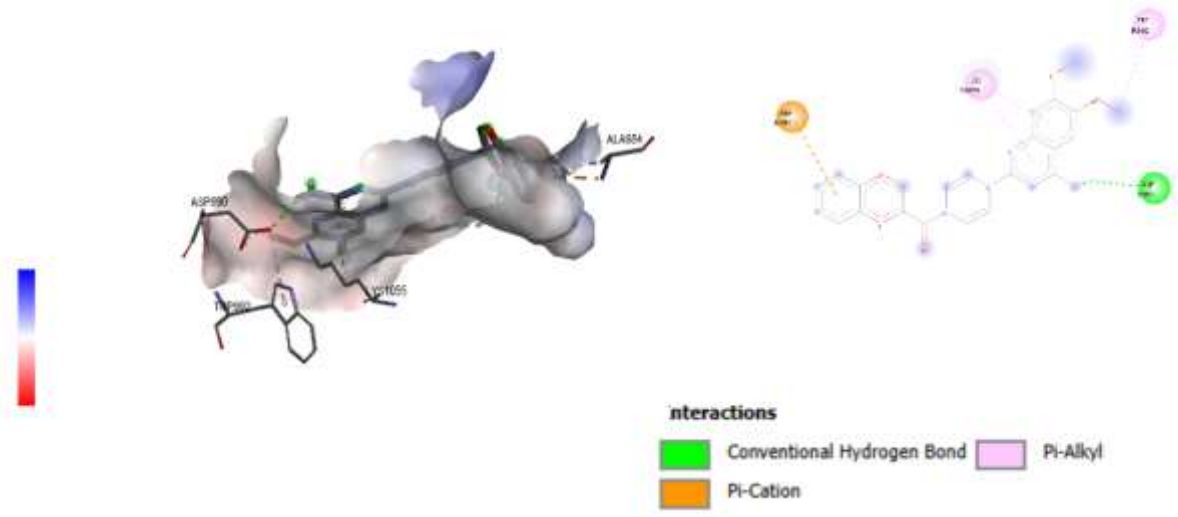

Figure 4. IGF1R interacted with Doxazosin Mesylate

The GPR83 has seven interacting residues with Doxazosin Mesylate. ALA:325, PHE:330, PRO:307, and ALA:329 are involved in Pi-alkyl interaction, as seen in Figure 5. TRP:332 and PHE:333 are involved in pi-pi

stacked interactions. And VAL:70 is involved in Pi-sigma. The receptor surface shows that the protein interaction locations illustrate neutralization.

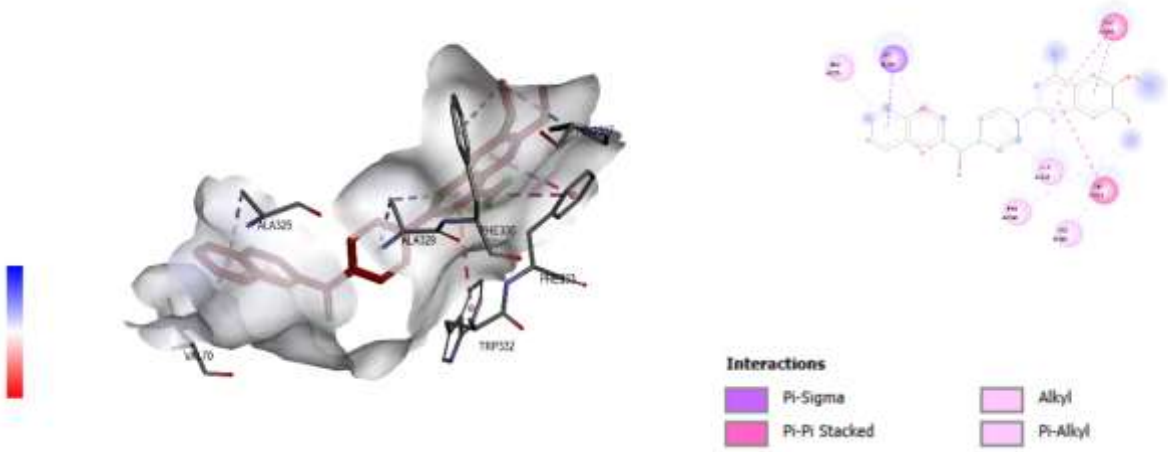

Figure 5. GPR83 interacted with Doxazosin Mesylate

2.4 Comparison between breast cancer and diabetes targeted candidates that target Doxazosin Mesylate

The docking analysis performed for both breast cancer-associated genes and diabetes-related genes revealed a significant difference in terms of their interactions with Doxazosin Mesylate, shown in Table 3, where it's clear that they had distinct binding patterns. It's important to emphasize the implications for therapeutic targeting pathway improvement. While it was expected to have better binding affinity of Doxazosin Mesylate against cancer-related candidates, there are still certain diabetic related genes that interfere with treatment resistance and breast cancer growth that should be focused on, which give a metastasis behavior of breast cancer cells [18].

Table 3. Comparative analysis of binding affinities of Cancer and diabetes-related genes using Doxazosin Mesylate

Breast cancer		**Diabetes**	
Protein	**GNINA Affinity (kcal/mol)**	**Protein**	**GNINA Affinity (kcal/mol)**
PIK3CA	-10.65	**IRS1**	-6.97
Akt1	-8.02	**IRS2**	-8.59
GSK3B	-9.2	**IGF1R**	-7.88
Mdm2	-9.23	**PRKCE**	-8.05
mTOR	-11.11	**GPR83**	-7.22
PIK3 delta	-8.56	**IRS4**	-5.69
S6K1	-9.67	**INSR**	-7.35

Although the cancer-related genes show a significant interaction with Doxazosin Mesylate, which has more physiological relevance and support the potential ligand to act as therapeutic strategy as anticancer drug, the diabetic genes still rising concern to interfere with breast cancer signaling pathway, were they have been reported the overexpression of insulin receptors in tumor cells, which activates specifically the downstream regulated signaling pathway, mainly PAM which has been studied and showed a strong comprehensive results. This evidence illustrates, meanwhile, Doxazosin Mesylate already has fascinating results; in order to ensure the

effectiveness of treatment, it's essential to shed light on other signaling pathways that crosstalk with it, which might change and differ the treatment responses and resistance pattern in different patients.

Among all cancer-diabetic-associated genes, IRS2 demonstrated the strongest binding affinity, which highlights the strong relevance in breast cancer therapeutic approaches. So, this comparison can conclude that it's not necessary to involve the diabetic genes as targeted candidates. However, it's important to take their biological consideration. Its ability to interact with metabolic-oncology crosstalk can influence. This can be a key to developing a combined therapeutic approach [8].

4. Conclusion

Overall, the in-silico study demonstrated a significant difference between breast cancer targets, mainly PI3K/AKT/mTOR candidates and diabetes related proteins that show an association with breast cancer gene using Doxazosin Mesylate. It confirms that Doxazosin Mesylate is a potent anticancer target against breast cancer pathways. However, it revealed weaker interactions, except for IRS2 and IGF1R, which have -8.59 kcal/mol and -8.05 kcal/mol, respectively, and revealed that insulin signaling pathway genes can support cell growth, survival, and proliferation. These are key mediators that can lead to cancer progression. This is not a direct therapeutic strategy, but rather emphasizes how crosstalk modulators can interfere with treatment response and resistance. Therefore, Doxazosin Mesylate is not a direct target for insulin-related genes, but its activity on these components can improve indirect cellular effects that can influence the nature of breast cancer tumors. Further investigation is needed to explore the impact of crosstalk and interconnected signaling pathways in breast cancer.

Declaration of competing interest

The authors declare that they have no known financial or non-financial competing interests in any material discussed in this paper.

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