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Research article

Molecular Docking Of Quercetin As An Anti-Breast Cancer Agent

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ABSTRACT

Background: Breast cancer is a major global health problem and a leading cause of death in women. Flavonoid compounds, particularly quercetin, have been extensively studied for their diverse pharmacological activities, including antioxidant, anti-inflammatory, and anticancer properties. Advances in computational technology in pharmaceutical and medicinal chemistry, particularly molecular docking, offer opportunities to predict interactions between ligands and target receptors quickly, efficiently, and at low cost. This study aimed to identify Molecular Docking Of Quercetin As An Anti-Breast Cancer Agent.
Methods: The ligand compounds were obtained from PubChem and the receptor clusters were obtained from the Protein Data Bank. Instrumens used VivoBook_AsusLaptop X409JB Intel ® Core ™ i3-1005G1 CPU @1.20GHz 12 RAM. The independent variables of this study were Quercetin and Doxorubicin to Cyclin-Dependent Kinase 6 (CDK6).
Results: Molecular docking results show that quercetin has an average binding affinity value of –6.19 kcal/mol, while the positive control doxorubicin has an average value of –7.3 kcal/mol against the Cyclin-dependent kinase 6 (CDK6) receptor. Amino acid similarities were found in the receptors for quercetin and doxorubicin. The same bound amino acids were found on the 3NUP, 3NUX, and 4EZ5 receptors with Van Der Walls Bond. Amino acid similarities were found in the receptors for quercetin and doxorubicin. The 4NUP receptor contains the same amino acids: Phenylalanine (A:164) and Histidine (A:143), while the 3NUX receptor contains Lysine (A:26), Valine (A:45), Valine (A:27), and Phenylalanine (A:164). Meanwhile, the 4EZ5 receptor has the same amino acids, namely Glycine (A:22), Glycine (A:20), and Asparagine (A:104). This indicates a similarity in the mechanisms of action between quercetin and doxorubicin.
Conclusion: Quercetin has great potential as a candidate for breast cancer treatment.

I. INTRODUCTION

Breast cancer is a significant global health concern, recognised as the leading cause of mortality among women worldwide. According to the Global Cancer Observatory, breast cancer accounts for a staggering 11.7% of all cancer cases, underscoring its prevalence and the urgent need for effective interventions (National Center for Biotechnology Information, 2025). The mortality rates associated with this disease remain alarmingly high, particularly in developing countries where access to healthcare resources and advanced treatment options can be severely limited (Chang, et al. 2023). Despite the availability of various therapeutic modalities, including chemotherapy, radiotherapy, and targeted therapy, these treatments often encounter formidable obstacles such as drug resistance, severe side

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effects, and prohibitive costs. Consequently, there is a pressing need for the discovery of new anticancer agents that are not only more effective but also selective and safe for patients (Butt, et al. 2018).

The complexity of breast cancer necessitates a multifaceted approach to treatment. Chemotherapy, for instance, while widely used, can lead to significant adverse effects, including nausea, hair loss, and increased susceptibility to infections. Radiotherapy, although effective in targeting tumours, can also damage surrounding healthy tissue, leading to long-term complications (Cahyanti, 2020). Targeted therapies, while promising, can be expensive and may not be accessible to all patients, particularly in lower-income regions. This situation highlights the critical need for innovative strategies in cancer treatment. One promising avenue is the exploration of natural-based approaches in the search for anticancer drugs.

Flavonoid compounds, particularly quercetin, have garnered considerable attention in recent years due to their diverse pharmacological activities (Hardjono, 2013). Quercetin, a plant-derived flavonoid, possesses a range of properties including antioxidant, anti-inflammatory, and anticancer effects. Its ability to inhibit cancer cell proliferation makes it a valuable candidate for further investigation. Research has shown that quercetin can induce apoptosis, or programmed cell death, in cancer cells, thereby preventing their unchecked growth. Additionally, it has been found to inhibit angiogenesis—the process by which new blood vessels form from existing ones—thereby starving tumours of the nutrients and oxygen they require for growth.

Several in vitro studies have provided compelling evidence of quercetin's efficacy against breast cancer. For example, experiments have demonstrated that quercetin can modulate critical signalling pathways such as PI3K/Akt, MAPK, and p53. The PI3K/Akt pathway is known to play a pivotal role in cell growth and survival, and its dysregulation is often associated with cancer. By targeting this pathway, quercetin may help to disrupt the survival signals that cancer cells rely on, leading to their eventual death. Similarly, the MAPK pathway is involved in the regulation of cell division, and its inhibition by quercetin could effectively halt the proliferation of cancerous cells. The p53 protein, often referred to as the "guardian of the genome," is crucial for maintaining cellular integrity. Quercetin's influence on this pathway further underscores its potential as an anticancer agent (Hasan, et al. 2022).

The advent of advanced computational technology in pharmacy and medicinal chemistry has revolutionised the field of drug discovery, particularly through the application of molecular docking techniques. Molecular docking offers a rapid, efficient, and cost-effective means to predict the interactions between ligands, such as quercetin, and target receptors associated with breast cancer. This computational method allows researchers to model the binding of quercetin to specific proteins involved in breast cancer, such as estrogen receptors (ER) and human epidermal growth factor receptor 2 (HER2) (Fristiohady, 2020). By simulating these interactions, molecular docking can provide valuable insights into the potential efficacy of quercetin as an anticancer agent, thereby guiding further experimental validation (Aryanti, et al. 2021).

For instance, the interaction between quercetin and estrogen receptors is particularly noteworthy, given the role of these receptors in the development and progression of hormone-dependent breast cancers. By binding to these receptors, quercetin may exert an inhibitory effect on the growth of cancer cells that rely on hormonal signals for proliferation (Morris, et al. 2009). Similarly, its interaction with HER2, a receptor that is overexpressed in a subset of breast cancers, could provide a novel therapeutic strategy for targeting these aggressive tumours.

In light of these findings, the current study aims to evaluate the potential of quercetin as an anti-breast cancer agent through a molecular docking approach (Yuliana, 2024). By leveraging computational techniques, this research seeks to elucidate the mechanisms by which quercetin may exert its anticancer effects, thereby supporting the development of more effective and safer natural-based drug candidates for breast cancer therapy. The hope is that, through this investigation, a clearer understanding of quercetin's interactions with critical cancer-related proteins will emerge, paving the way for future clinical applications (Geleta and Makonnen, 2016).

Breast cancer remains a formidable health challenge worldwide, necessitating the continuous search for innovative treatment options. The exploration of natural compounds such as quercetin presents a promising avenue for the development of safer and more effective therapies. By integrating molecular docking techniques with experimental research, we can gain deeper insights into the potential of quercetin as an anticancer agent. This multifaceted approach not only enhances our understanding of

breast cancer biology but also holds the promise of improving patient outcomes in the fight against this pervasive disease. As we move forward, it is essential to continue exploring the vast potential of natural compounds in the quest for effective cancer treatments, ultimately striving for a future where breast cancer can be managed more effectively and with fewer side effects.

II. METHODS

This study employed an experimental approach using in silico techniques, referring to research conducted through computer simulations and available databases. Instrumens used VivoBook_AsusLaptop X409JB Intel ® Core ™ i3-1005G1 CPU @1.20GHz 12 RAM. Molecular docking tools were used to analyze the interactions between the active compounds Quercetine and the CDK6 (Cyclin-dependent kinase 6) receptor, a breast cancer therapy target that inhibits cell proliferation via phosphorylation of the retinoblastoma protein. Comparisons were made with the standard drug doxorubicin using software such as AutoDock Tools, BIOVIA Discovery Studio to assess binding affinities.

III. RESULTS

The results of breast cancer receptor searches on Cyclin-Dependent Kinase 6 (CDK6) from the Protein Data Bank yielded 3NUP, 3NUX, 2EUF, 4EZ5, 8I0M, 5L2I, 5L2S, and 4TTH.

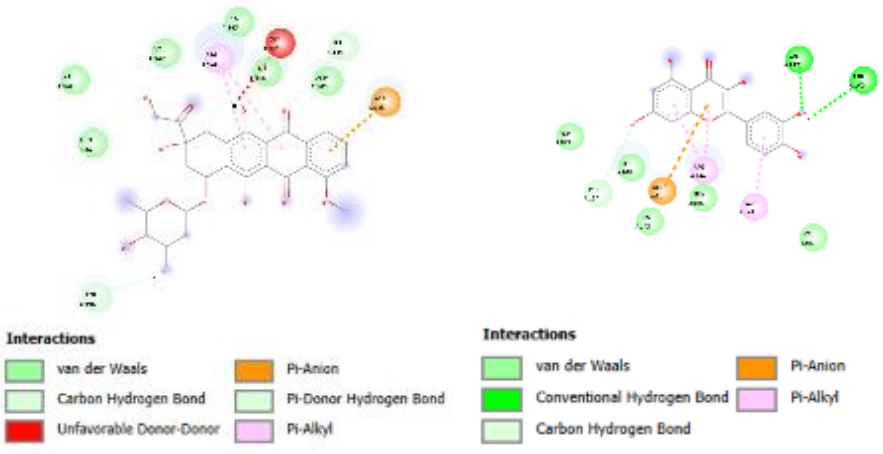
Molecular docking results show that quercetin has an average binding affinity value of –6.19 kcal/mol, while the positive control doxorubicin has an average value of –7.3 kcal/mol against the Cyclin-dependent kinase 6 (CDK6) receptor. A more negative binding affinity value indicates a more stable and stronger ligand–receptor interaction. The molecular docking results can be seen in the table 1.

Table 1. Molecular docking Quercetine and Doxorubicin

NO	RECEPTOR	BINDING AFFINITY (kcal/mol)	
		QUERCETINE	DOXORUBICIN
1	2EUF	-5.2	-7.9
2	3NUP	-6.2	-6.8
3	8I0M	-6.6	-6.9
4	3NUX	-7.0	-8.1
5	4EZ5	-6.7	-7.6
6	4TTH	-5.1	-7.3
7	5L2S	-6.4	-7.4
8	5L2I	-6.3	-7.0
	Average	**-6.19**	**-7.38**

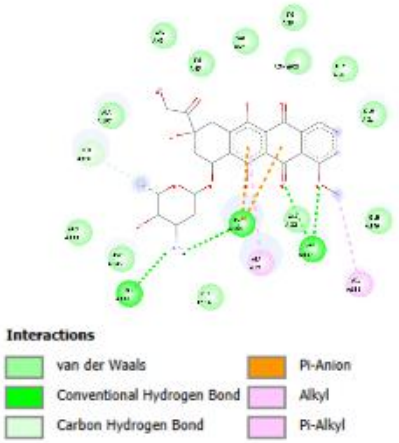
Visualization of ligand interaction with CDK6 protein using Discovery Studio Visualizer software is shown in Figure 1.

A. **Receptor : 3NUP**

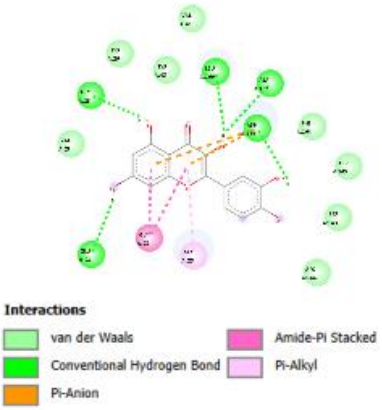


i. Doxorubicin ii. Quercetine

B. **Receptor : 3NUX**

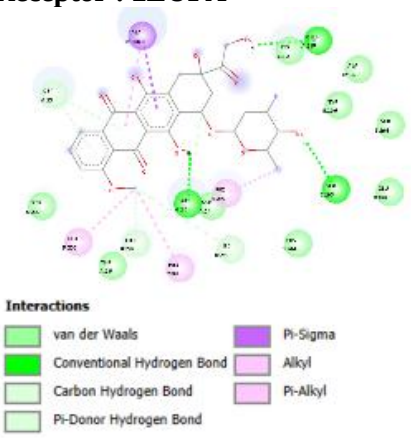


i. Doxorubicin

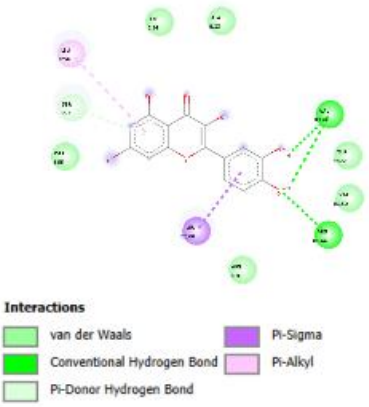


ii. Quercetine

C. **Receptor : 2EUFA**

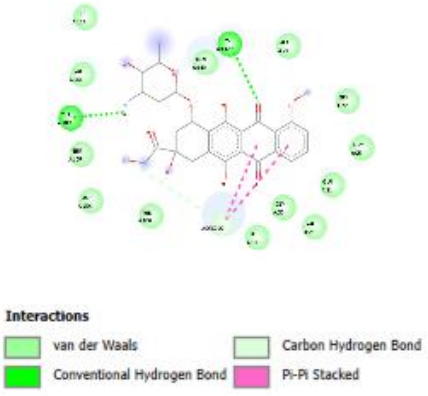


i. Doxorubicin

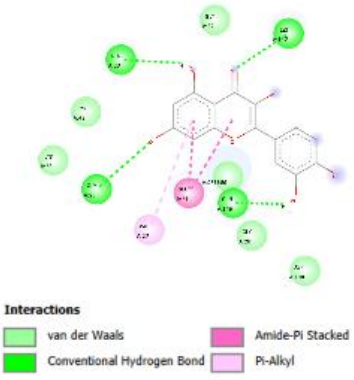


ii. Quercetine

D. **Receptor : 4EZ5**

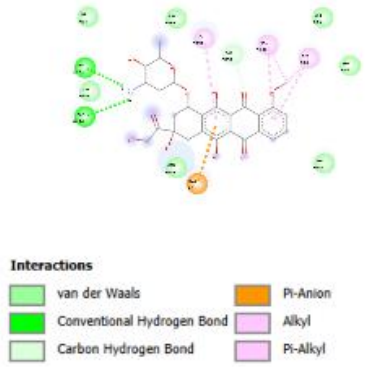


i. Doxorubicin

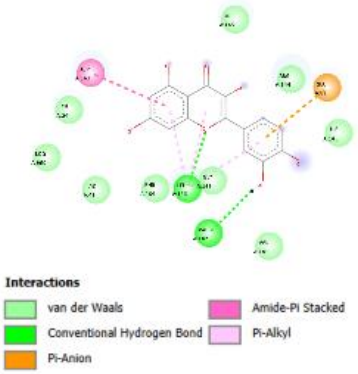


ii. Quercetine

E. **Receptor : 5L2I**

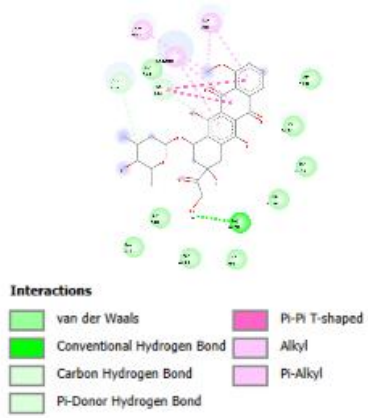


i. Doxorubicin

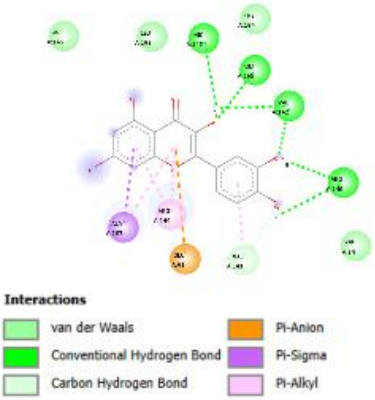


ii. Quercetine

F. **Receptor : 5L2S**

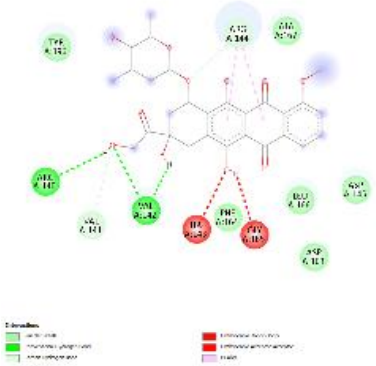


i. Doxorubicin

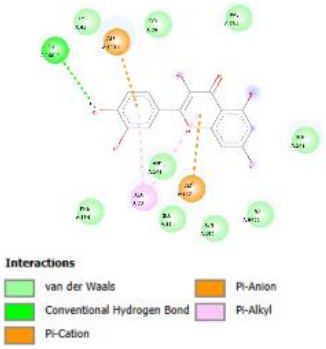


ii. Quercetine

G. **Receptor : 8I0M**

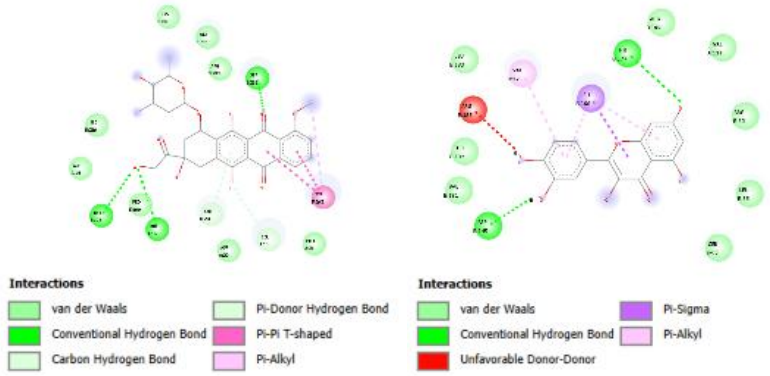


i. Doxorubicin



ii. Quercetine

H. **Receptor : 4TTH**



i. Doxorubicin ii. Quercetine

Figure 1. Interaction Doxorubicin and Quercetine with CDK6 protein

Amino acid similarities were found in the receptors for quercetin and doxorubicin. The same bound amino acids were found on the 3NUP, 3NUX, and 4EZ5 receptors with Van Der Walls Bond. The comparison of the bonds between quercetin and doxorubicin can be seen in Table 2.

Table 2. Ligand and protein bonds and bound amino acids to Quercetine and Doxorubicin

		Amino Acid	
Receptor	**Bound**	**Quercetin**	**Doxorubicin**
3NUP	Van der Waals	**PHE A:164, HIS A:143** ASP A:163	VAL:A:141, AL:A:142, GLU:A:61, **HIS:A:143, PHE:A:164**
3NUX	Van der Waals	**LYS A:26**, LYS A:43 **VAL A:45, VAL A:27** ALA A:67, **PHE A:164** ASP A:145, HIS A:143 ARG A:144	**LYS:A:26, VAL:A:27**, ASN:B:00, GLY:A:20, GLU:A:21, **VAL:A:45,** ALA:A:167, LEU:A:166, **PHE:A:164**, GLN:A:149, VAL:A:181
4EZ5	Van der Waals	**GLY A:22**, LYS A:43 LYS A:26, **GLY A:20 ASP A:104**	TRP:A:184, VAL:A:181, THR:A:107, **ASP:A:104,** THR:A:106, ALA:A:23, GLU:A:21, **GLY:A:20**, VAL:A:27, **GLY:A:22**, GLY:A:25, GLN:A:149

The 4NUP receptor contains the same amino acids: Phenylalanine (A:164) and Histidine (A:143), while the 3NUX receptor contains Lysine (A:26), Valine (A:45), Valine (A:27), and Phenylalanine (A:164). Meanwhile, the 4EZ5 receptor has the same amino acids, namely Glycine (A:22), Glycine (A:20), and Asparagine (A:104)

IV. DISCUSSION

Molecular docking results show that quercetin has an average binding affinity value of –6.19 kcal/mol, while the positive control doxorubicin has an average value of –7.3 kcal/mol against the Cyclin-dependent kinase 6 (CDK6) receptor. A more negative binding affinity value indicates a more stable and stronger ligand–receptor interaction.

CDK6, or Cyclin-Dependent Kinase 6, plays a pivotal role in the regulation of the cell cycle, particularly during the critical transition from the G1 phase to the S phase. This transition is essential for cellular proliferation, as it marks the point where cells prepare to replicate their DNA. The activation of CDK6 is intricately linked to the proliferation of breast cancer cells, thereby making it a significant target for therapeutic intervention in cancer treatment (Patologi, et al. 2019). Inhibiting the activity of CDK6 presents a promising strategy for slowing down or halting the growth of cancerous cells, particularly in

the context of breast cancer, where the dysregulation of cell cycle control is often observed (Diukendjieva, et al. 2017).

The exploration of ligands that can interact effectively with CDK6 is therefore of paramount importance. Such ligands have the potential to inhibit breast cancer cell growth by disrupting the normal function of CDK6. Among the compounds studied, doxorubicin and quercetin stand out due to their distinct binding affinities and mechanisms of action (Ferreira, et al. 2015). Doxorubicin, a well-established chemotherapy drug, exhibits a binding affinity value of -7.3 kcal/mol for CDK6, which is significantly lower than that of quercetin, which has a binding affinity of -6.19 kcal/mol. This difference in binding affinity suggests that doxorubicin interacts more strongly with CDK6 compared to quercetin, aligning with its established efficacy in various cancer therapies, including those targeting breast cancer.

To illustrate this point, consider the clinical application of doxorubicin. It is commonly administered in combination with other chemotherapeutic agents to enhance its effectiveness against a range of cancers (Cahyanti, 2020). Its robust binding to CDK6 contributes to its ability to inhibit cell cycle progression, ultimately leading to reduced tumour growth. However, the strength of doxorubicin's interaction with CDK6 also raises concerns regarding its toxicity, as the drug is notorious for causing a range of side effects, including cardiotoxicity and myelosuppression (Rognan, 2017). This highlights the need for alternative therapeutic strategies that can provide effective cancer treatment with reduced adverse effects.

On the other hand, quercetin, a natural flavonoid compound found in various fruits and vegetables, presents an intriguing alternative. Although its binding affinity is not as strong as that of doxorubicin, the proximity of its binding affinity value suggests that quercetin may still exert significant inhibitory effects on CDK6. The fact that quercetin is a naturally occurring compound is particularly advantageous, as it is generally associated with lower toxicity and fewer side effects compared to conventional chemotherapy drugs (Diwan, 2017). This characteristic positions quercetin as a potential candidate for development as a complementary or adjuvant agent in breast cancer therapy.

Delving deeper into the molecular interactions that underpin the binding of these compounds to CDK6, we find that the stability of the binding interaction is influenced by various factors, including the nature of the amino acid residues involved. For instance, the analysis of amino acid residue interactions, such as hydrogen bonds, π-π interactions, and hydrophobic bonds, provides insight into how these compounds engage with CDK6 (Fristiohady, 2020) Quercetin, with its polyphenolic structure rich in hydroxyl (-OH) groups, is capable of forming multiple hydrogen bonds with polar amino acid residues located at the active site of CDK6. This interaction is crucial for maintaining the structural integrity of the binding complex, even if the overall binding affinity is lower compared to doxorubicin.

In contrast, doxorubicin, which belongs to the anthracycline class of drugs, features a broad aromatic ring that facilitates the formation of stable π-π stacking interactions and hydrophobic bonds. These interactions contribute to the overall strength of doxorubicin's binding affinity to CDK6, allowing it to effectively inhibit the kinase's activity. The presence of these stabilising interactions is a key factor in the drug's potency as an anticancer agent. However, the strong binding affinity of doxorubicin also correlates with its significant side effects, underscoring the trade-off between efficacy and safety in cancer treatment (Sari, 2020).

From these analyses, it becomes evident that while quercetin may not possess the same level of potency as doxorubicin, it still demonstrates considerable potential as an anticancer candidate through its mechanism of CDK6 inhibition. The natural origin of quercetin not only suggests a lower toxicity profile but also opens avenues for its use in combination therapies aimed at enhancing the efficacy of existing treatments while mitigating their adverse effects (Muflihunna and Syarif, 2023). The potential for quercetin to act as an adjuvant agent in breast cancer therapy is particularly compelling, as it could help alleviate some of the side effects associated with standard chemotherapy drugs, such as doxorubicin. Moreover, the biological activity of quercetin extends beyond its interaction with CDK6. Research has indicated that quercetin possesses a range of anticancer properties, including antioxidant effects, anti-inflammatory activities, and the ability to modulate various signalling pathways involved in cancer progression (Sherr, 2016). These multifaceted mechanisms further bolster the case for quercetin as a valuable addition to breast cancer treatment regimens.

The comparative analysis of doxorubicin and quercetin in their interaction with CDK6 reveals critical insights into their potential roles in cancer therapy. Doxorubicin's stronger binding affinity

underscores its established efficacy in treating breast cancer, yet it is tempered by significant toxicity concerns. Conversely, quercetin, while exhibiting a lower binding affinity, presents a promising alternative due to its natural origin and lower toxicity profile. The possibility of quercetin serving as a complementary or adjuvant agent in breast cancer therapy highlights the importance of exploring natural compounds in the quest for effective and safer cancer treatments. Future research should focus on validating these findings through in vitro and in vivo studies to fully elucidate the therapeutic potential of quercetin in the context of breast cancer and beyond.

V. CONCLUSION

Quercetin has the potential to be an adjuvant agent or natural anticancer candidate with a CDK6 inhibition mechanism.

VI. CONFLICTS OF INTEREST

No conflict of interest.

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