COMPUTATIONAL EVALUATION OF GINSENOSIDES AS ALTERNATIVE THERAPEUTIC AGENTS TARGETING THE BREAST CANCER-ASSOCIATED BARD1 GENE: MOLECULAR DOCKING AND ARTIFICIAL INTELLIGENCE APPROACHES

Nil SAZLI, Deniz KARATAŞ
Manisa Celal Bayar University, Faculty of Engineering And Natural Sciences, Department of Bioengineering

***Abstract*—Breast cancer associated with the BARD1 gene occurs when the cell cycle in breast tissue becomes abnormal and proliferates uncontrollably. The increasing incidence of breast cancer, particularly in recent years, has become a significant public health concern. This study investigates the potential of ginsenosides derived from the *Panax ginseng* plant, known for their anticancer bioactive properties, as alternative drug candidates to chemical synthetic agents in breast cancer treatment. Within the scope of the study, the crystal structure of the BARD1 gene (PDB ID: 3C5R) receptor, along with Ginsenoside Rk1, Ginsenoside Ro, Pseudoginsenoside Rt5, and Vinaginsenoside R3 ginsenosides, as well as the reference drugs 5-Fluorouracil (5FU), Carboplatin, Docetaxel, and Ixabeliplane, were subjected to molecular docking to evaluate their potential anticancer bioactive activities and binding affinities to the BARD1 receptor. An artificial intelligence-based (AI-based) model was developed to optimize the binding energy between the receptor and the ligands in question, and the docking process was repeated to select the best receptor-ligand complex. This hybrid methodology improves the accuracy of binding score predictions for complex and flexible natural compounds. Our study is among the first to investigate the interactions of ginsenosides with the breast cancer-associated BARD1 protein using a hybrid methodology that combines classical and AI-based molecular docking approaches. The most promising potential drug candidate among the receptor-ligand complexes was identified, and its pharmacokinetic properties were evaluated using ADMET analyses. According to the findings, while Docetaxel (-9.5 kcal/mol) exhibited the highest binding affinity among chemical agents, natural ginsenosides such as Ginsenoside Ro (-9.5 kcal/mol) and Ginsenoside Rk1 (-9.0 kcal/mol) demonstrated binding affinities comparable to the reference ligands. Based on artificial intelligence-based molecular docking binding energy predictions, the receptor-ligand complexes formed with Ginsenoside Ro (-8.54 kcal/mol) and Carboplatin (-9.82 kcal/mol) achieved the best scores. The results of this study indicate that *Panax ginseng*-derived ginsenosides exhibit binding energies similar to those of chemical compounds against the BARD1 gene receptor associated with breast cancer. These findings are highly promising for preclinical studies, supporting the potential evaluation of ginsenosides as natural alternatives in breast cancer treatment.**

***Index Terms*- Docking, Artificial intelligence, Breast cancer, Ginsenoside, Bard1, h-bond**

I. INTRODUCTION

Breast cancer, which has become increasingly prevalent in recent years and poses a significant threat to women's health, occurs when cells in the breast tissue undergo uncontrolled proliferation due to dysregulation of the cell cycle caused by various factors [1, 2]. Identifying critical genes and molecular mechanisms involved in breast cancer progression and essential for cell cycle regulation is crucial for the development of alternative therapeutic strategies [3]. The BARD1 gene, which is specifically associated with breast cancer, interacts with BRCA1 and exhibits tumor suppressor properties. These two gene-encoded proteins dimerize to form a heterodimeric complex [3]. Due to the homologous regions present in both structures, it regulates the cell cycle and plays a crucial role in the DNA damage repair mechanisms [4]. Understanding the molecular mechanisms of this gene is essential for ensuring the proper completion of the cellular and DNA cycle in breast cancer without damage [5]. While exploring alternative therapeutic strategies for challenging diseases such as breast cancer, it is crucial to investigate related structures like the BARD1 gene, analyze gene and drug components in three dimensions using molecular modeling approaches, and examine protein-ligand interactions to gain a deeper understanding of the complex mechanisms underlying breast cancer [5, 6]. In this way, the interaction profiles of the BARD1 gene with different ligands can be comprehensively analyzed, and binding energies can be obtained, thereby facilitating the rational design of new potential drug compounds of natural origin that can be targeted for breast cancer treatment [7].

While significant drug and treatment discovery studies for breast cancer are being conducted, recent years have seen a growing focus on the use of techniques such as artificial intelligence (AI) and machine learning (ML) [8]. In particular, modeling techniques such as molecular docking represent a crucial methodological step in computational discovery processes. Traditional molecular modeling algorithms perform calculations based on static physical principles governing the binding energies between receptors and ligands [9]. However, large and complex receptor–

(Corresponding author: Deniz Karataş).
Nil Sazlı, Manisa Celal Bayar Üniversitesi, Mühendislik ve Doğa Bilimleri Fakültesi, Biyomühendislik Bölümü, Manisa, Türkiye.
(e-mail: 231208005@ogr.cbu.edu.tr).
Deniz Karataş, Manisa Celal Bayar Üniversitesi, Mühendislik ve Doğa Bilimleri Fakültesi, Biyomühendislik Bölümü, Manisa, Türkiye.
(e-mail: deniz.karatas@cbu.edu.tr).

ligand systems may result in the omission of nonlinear and dynamic interactions [9, 10]. As an alternative to traditional methodologies, AI-based docking models enable the use of artificial neural networks trained on large datasets and provide highly accurate predictions of receptor–ligand binding affinities [11]. Studies in the literature demonstrate that deep learning models employing molecular fingerprints and 3D spatial data significantly enhance the reliability of binding score calculations in molecular docking [12]. The use of AI, which is becoming increasingly widespread across scientific disciplines, particularly in integration with molecular modeling techniques like molecular docking, enables comprehensive analyses in drug development processes, including ligand prioritization, pharmacophore alignment, and binding specificity [13]. For these reasons, optimizing the binding scores obtained through classical docking using an artificial neural network (ANN) model in our study has enhanced the statistical reliability of our findings and yielded highly robust binding predictions in biological terms [14].

In our study, the binding interactions of natural ginsenosides—Ginsenoside Ro, Ginsenoside Rk1, Pseudoginsenoside Rt5, and Vinaginsenoside R3—derived from *Panax ginseng* with the BARD1 gene were investigated by optimizing them using classical molecular docking and artificial intelligence-supported molecular docking methods. These interactions were compared with widely used chemotherapeutic agents, including 5-Fluorouracil (5-FU), Carboplatin, Docetaxel, and Ixabepilone, in the context of breast cancer treatment. ADMET analysis was conducted to assess the pharmacokinetic properties and drug potential of ginsenosides. The primary reason for selecting these natural ginsenosides in this study is their well-documented biochemical effects, which include activating apoptotic mechanisms in breast cancer cells, inhibiting proliferation, and preventing metastatic spread [15]. The selection of 5-FU, Carboplatin, Docetaxel, and Ixabepilone as control ligands, representing synthetic chemical agents, is due to their widespread use in breast cancer treatment and their mechanism of action, which involves inhibiting cancer cell division and DNA synthesis [16, 17]. Comparing ginsenosides with chemotherapeutic agents using molecular docking techniques and analyzing their binding energies and interaction mechanisms with the BARD1 gene facilitates the rational design of pharmacological alternatives for the discovery of natural agents with high target specificity. Furthermore, this study lays the groundwork for preclinical research and contributes to the scientific literature by proposing a novel methodology and identifying promising natural agents for breast cancer treatment.

II. MATERIALS AND METHODS

A. Ligand Selection

Natural ginsenosides—Ginsenoside Ro (PubChem CID: 11815492), Ginsenoside Rk1 (PubChem CID: 11499198), Pseudoginsenoside Rt5 (PubChem CID: 21633075), and Vinaginsenoside R3 (PubChem CID: 92043620)—and synthetic drugs, including 5-Fluorouracil (5-FU, PubChem CID: 3385), Carboplatin (PubChem CID: 426756), Docetaxel (PubChem CID: 148124), and Ixabepilone (PubChem CID: 6445540), which are commonly used in both adjuvant and neoadjuvant breast cancer therapies were selected as ligands. The ligands were identified through a comprehensive literature search using databases such as Open Targets (https://www.opentargets.org/) and the National Center for Biotechnology Information (NCBI, PubMed). Ligand structures were retrieved from the PubChem database (http://pubchem.ncbi.nlm.nih.gov/) web server.

B. Molecular Docking

The crystal structure of the BARD1 gene (PDB ID: 3C5R) was selected as the receptor and retrieved from the Protein Data Bank (PDB). AutoDock Vina was used to calculate binding affinities between ligands and the receptor. Chimera 1.17.3 software was utilized to prepare the receptor and ligands for the docking process. Water molecules were removed from the receptor structure. After polar hydrogens were added Gasteiger charges were assigned. Subsequently, energy minimization was performed to optimize the atomic positions within the receptor structure, and the receptor was prepared for the docking process [18]. In order to prepare the ligands for the docking stage, each ligand was loaded into the Chimera 1.17.3 software, and the structures were energy-minimized by setting AMBER as the force field and defining the number of steps as 100 [19]. The geometric center and XYZ coordinate parameters used in the docking stage were calculated using the AGFR program, with the determined center coordinates being X: 8.871, Y: 18.902, Z: 31.783. Considering the volume of the ligands, the grid box dimensions were set to 30×30×30, 40×40×40, 50×50×50, and 60×60×60 based on the respective ligands [20, 21]. At the end of all these stages, each ligand and receptor were subjected to docking for each grid size using the Chimera 1.17.3 software. A total of 32 different conformations were generated to identify the optimal binding energy. The 2D interaction diagrams of the different protein-ligand conformations obtained after docking were visualized using the Discovery Studio 2024 Client software [22]. The types of bond interactions formed between the ligands and the BARD1 protein with the lowest binding energy were analyzed using the generated diagram.

C. Molecular Docking with Artificial Intelligence

In our study, due to the limitations of the classical molecular docking technique—which relies solely on static energy-based scoring functions—optimization was performed using an artificial neural network (ANN) model [11]. Leveraging the chemical descriptors and spatial parameters provided by this artificial intelligence-based approach enables more accurate predictions of the binding interactions in complex receptor–ligand systems. Notably, the hybrid methodology developed with the ANN model

yielded more reliable results for steric clashes and three-dimensional structural mismatches, which are often overlooked in conventional docking methods, making this strategy preferable [12]. At this stage, docking performance was optimized based on molecular docking scores obtained using an artificial intelligence-based application. Additionally, the binding scores from each docking operation performed using Chimera 1.17.3 were predicted with an artificial neural network model implemented using the PyTorch library in the Google Colab interface [9, 23]. Receptor and ligand structures previously prepared using Chimera 1.17.3 software were uploaded to Google Colab with the RDKit library. In this step, the SMILES (Simplified Molecular Input Linear Representation) formats of the ligands were retrieved from the PubChem database and uploaded to the Colab environment to facilitate molecular fingerprint generation. Molecular fingerprints of the structures were calculated and converted into tensors [13]. The previously determined grid box dimensions, geometric center, and XYZ coordinate parameters were incorporated into the model using AGFR. Then, an artificial neural network model consisting of three layers was constructed. The designed model first predicts the binding score by integrating the molecular fingerprints and grid parameters of the receptor and ligand molecules [12]. For training the model, the Adam optimization algorithm was used to compute the binding scores and optimize the parameters in Chimera 1.17.3 software. The model was trained using the Adam optimizer over 100 epochs, with performance evaluated at every 10th epoch [9].

III. RESULTS AND DISCUSSIONS

Molecular docking is widely used in drug development to calculate the binding energies between target receptors and ligands, as well as to analyze the interactions formed between them [24]. It particularly highlights the therapeutic potential of compounds in complex structures with binding energies lower than -6.5 kcal/mol [25]. In literature studies targeting receptors containing BRCT domains, such as BARD1, it has been observed that proteins associated with DNA repair exhibit binding scores significantly lower than the aforementioned value and demonstrate good biological activity [6]. In this study, the binding affinities of the natural agent ginsenoside and neoadjuvant and adjuvant chemical drugs used in breast cancer with the crystal receptor structure (PDB ID: 3C5R), which is associated with the BARD1 gene, as presented in Table 1, were calculated using both traditional docking and an artificial intelligence-based model across different grid sizes according to the volume of the ligands.

TABLE I
BINDING AFFINITY SCORES OF LIGANDS AT DIFFERENT GRID SIZES AND AI-PREDICTED DOCKING SCORES (KCAL/MOL)

Ligands	**Binding Affinity Scores (kcal/mol)**				
	30x 30x30 Grid Size	**40x 40x40 Grid Size**	**50x 50x50 Grid Size**	**60x 60x60 Grid Size**	**Predicted Score***
Ginsenoside Ro	-9.4	-9.4	-9.4	-9.5	-8.5408
Ginsenoside Rk1	-8.4	-9	-8.5	-8.5	-8.1736
Pseudoginsenoside Rt5	-8.9	-8.9	-8.8	-8.8	-7.7835
Vinaginsenoside R3	-8.3	-8.4	-8.4	-8.4	-7.5056
5-FU	-4.4	-4.5	-4.3	-4.5	-4.6568
Carboplatin	-4.6	-4.6	-4.6	-4.6	-9.8218
Docetaxel	-8.9	-8.8	-8.2	-8	-8.2291
Ixabelipone	-8.4	-8	-8	-8	-6.9089

***** Considering the highest binding affinity scores (kcal/mol) and grid parameters obtained from the receptor-ligand docking study conducted using the UCSF Chimera 1.17.3 software, an artificial intelligence-based model was developed on the Google Colab web server. Using this model, docking scores were optimized, and predicted scores were generated.

In Table 1, the grid sizes corresponding to the lowest binding energy scores calculated via the traditional docking method were selected, and docking was performed using these sizes in the artificial intelligence-based model. This grid box parameter-based methodology is utilized to improve the precision of ligand conformations and to better define molecular dimensions [21]. According to the findings of the study, the target receptor BARD1 gene exhibited the lowest binding scores with Ginsenoside Ro (-9.5 kcal/mol), Ginsenoside Rk1 (-9.0 kcal/mol), Pseudoginsenoside Rt5 (-8.9 kcal/mol), and Vinaginsenoside R3 (-8.4 kcal/mol), while the synthetic ligands 5-FU (-4.5 kcal/mol), Carboplatin (-4.6 kcal/mol), Docetaxel (-8.9 kcal/mol), and Ixabepilone (-8.4 kcal/mol) demonstrated comparable values. Particularly, the high binding affinities of Ginsenoside Ro and Ginsenoside Rk1 are attributed to their rich structural profiles, characterized by glycosidic bonds, multiple hydroxyl groups, and a rigid steroidal backbone. The BARD1 receptor utilized in this study is also a significant factor influencing binding affinity. Key polar amino acid residues within the binding pocket of this receptor facilitate hydrophilic interactions and the formation of multiple conventional

hydrogen bonds. The expansion of solvation and interaction surface areas via the glycosidic moieties enables proper ligand orientation on the receptor and promotes highly stable binding. This binding behavior is consistent with previous literature, which has demonstrated that ginsenosides exhibit strong affinity toward proteins such as BARD1—known to be involved in the DNA damage repair mechanism associated with breast cancer—due to their conformational rigidity and amphiphilic nature, allowing selective binding to polar cavities within the active site [4, 5]. The predicted docking scores were obtained by optimizing docking calculations using the artificial intelligence-based model with the grid box parameters derived from these results. The predicted scores were estimated as -8.5408, -8.1736, -7.7835, -7.5056, -4.6568, -9.8218, -8.2291, and -6.9089 kcal/mol, respectively. In general, an examination of the traditional docking scores revealed that the natural agent ginsenosides exhibited binding scores comparable to those of chemical drugs, and in some cases, even lower. This observation suggests that natural agents, which exhibit significantly lower toxicity compared to chemical drugs, could serve as a promising alternative therapeutic solutions with high bioavailability for the treatment of BARD1-related breast cancer. [26]. Additionally, the crystal structure of the BARD1 gene (PDB ID: 3C5R) indicates that ginsenosides exhibit strong binding affinity to its receptor. This finding provides preliminary insights into the stability of the binding interaction [27]. The main purpose of comparing the results with traditional docking using an AI-based model is to save time and increase resource efficiency by screening the interactions between the target receptor and ligand in a large library in a shorter time [12, 28]. Additionally, optimization is performed to ensure the reliability of the binding affinity scores of the receptor-ligand complex. The docking scores obtained from traditional docking and the artificial intelligence-based model are generally in close agreement [29]. However, in traditional docking methods performed using program-based algorithms, a fixed approach is employed to calculate binding energies, leading to a standardized computation time [12, 29]. In contrast, artificial intelligence-based models, trained on comprehensive datasets, yield more accurate findings compared to traditional methods by analyzing the binding energies of receptor-ligand complexes in greater detail. AI-driven methods provide an innovative perspective in drug discovery by enhancing both the accuracy and speed of docking techniques. It enhances the reliability of binding predictions by capturing subtle conformational dynamics that are typically not accounted for by the static scoring functions of AI models, particularly in structures containing flexible glycosidic bonds such as natural ginsenosides, where static scoring functions used in classical molecular docking often fail to capture conformational variations [8, 12].

D. Molecular Binding Interactions of Natural and Synthetic Ligands with the BARD1 Receptor

Binding interaction maps facilitate the analysis of ligand interactions with amino acid residues in the target receptor, the types of interactions formed, the stability of the receptor-ligand complex, and the evaluation of biological activity [30]. In Figure 1, the binding modes of the receptor-ligand complexes formed with the target receptor (PDB ID: 3C5R) in the BARD1 gene after ligand docking are presented. Analysis of the interaction maps of the obtained receptor–ligand complexes reveals that hydrogen bonding is the most dominant type of interaction. This is primarily attributed to the structural composition of ginsenosides, which are rich in glycoside, polysaccharide, and hydroxyl groups, as well as the presence of carbonyl (-C=O), amine (-NH), and hydroxyl (-OH) functional groups, which are essential for hydrogen bond formation [31, 32]. Conventional hydrogen bond formation plays a crucial role in the stability of the receptor-ligand complex, as hydrogen bonds facilitate the prolonged retention of the ligand within the receptor's binding site, thereby enhancing its biological effect on the receptor [17]. In our study, hydrogen bond formation demonstrates that ginsenosides and synthetic agents specifically bind to the BARD1 receptor [33, 34]. This finding indicates that ginsenosides have potential as drug candidates. Upon examining the binding modes in Figure 1, the amino acids LYS (B:503), ASN (B:504), GLY (A:505), HIS (A:506), ASP (A:508), and THR (A:534) are consistently observed in the interaction map of nearly every ligand. These recurrent amino acids specifically define the binding sites of the BARD1 receptor, highlighting the specificity of the active site. Additionally, these amino acids contribute to the stabilization of ginsenosides on the BARD1 receptor by facilitating hydrogen bond formation [35]. The verification of specific binding sites and amino acids of receptors in an *in silico* environment using molecular docking techniques and 3D visualization accelerates rational drug design in drug development studies. This approach facilitates the development of high-affinity drugs, contributing to the discovery of alternative therapeutic strategies for challenging diseases such as breast cancer.

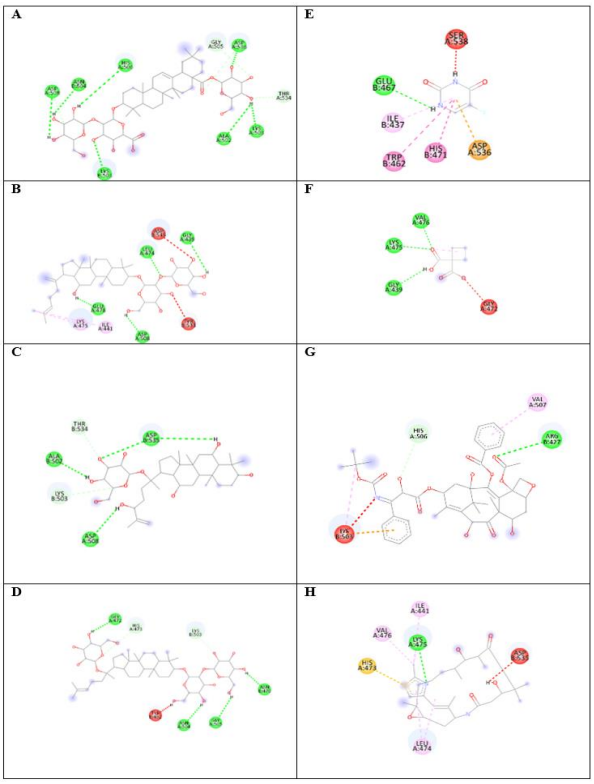

FIGURE 1. Molecular interactions between the receptor of the bard1 gene (pdb ıd: 3c5r) and ginsenosides (a: ginsenoside ro, b: ginsenoside rk1, c: pseudoginsenoside rt3, d: vina gınsenosıde r3) and synthetic chemotherapeutic agents (e: 5-fu, f: carboplatin, g: docetaxel, h: ixabepilone) were investigated. Binding interactions between the receptor and ligands were visualized in 2d. green dashed lines indicate hydrogen bonds, red dashed lines indicate negative interactions, and pink and purple interactions indicate hydrophobic and π-related contacts.

E. ADMET Profiling and Pharmacokinetic Predictions

The pharmacokinetic and pharmacodynamic properties of bioactive ligands, considered potential drug candidates, are determined through ADMET analyses, which assess absorption, distribution, metabolism, excretion, and toxicity [36]. Table 2 presents the pharmacokinetic properties of natural ginsenosides in comparison with synthetic drugs to evaluate their drug potential. When examining the solubility (Log S) and absorption profiles (HIA Absorption) of the ligands, as expected, the solubility of widely used synthetic ligands, 5-FU (-1.17 log mol/L) and Carboplatin (-0.761 log mol/L), is significantly higher than that of ginsenosides. However, considering the long and complex chemical structures of ginsenosides, solubility values ranging from -3.700 to -4.114 log mol/L are interpreted as relatively favorable. This finding indicates that ginsenosides exhibit sufficient pharmacological activity through active transport mechanisms and membrane permeability, despite their low solubility and high molecular weight, which is consistent with previously reported literature [37]. In terms of human intestinal absorption (HIA), ginsenosides exhibit low to moderate absorption levels, similar to synthetic drugs [38]. This finding suggests that ginsenoside-based agents could serve as a natural alternative, particularly for breast cancer treatment, as they exhibit absorption levels comparable to other drugs [39]. When examining the pharmacokinetic properties related to the ~~Blood-Brain Barrier~~ blood-brain barrier (BBB), it is observed that the control group drugs exhibit BBB permeability. Since BBB permeability is a crucial parameter for preventing brain metastases, possessing this characteristic is highly significant for a compound with drug potential [40]. Pseudoginsenoside Rt5 and Vinaginsenoside R3 ginsenosides exhibit BBB permeability, making these natural ligands valuable for reaching the central nervous system and preventing the spread of breast cancer metastases to the brain. P-glycoprotein (P-gp) is a carrier protein that facilitates the efflux of drugs from cells in the human body. The presence of this protein as a substrate has the potential to reduce bioavailability by promoting drug excretion, thereby diminishing drug efficacy [41]. In this context, the presence of a P-gp substrate is not a desirable pharmacokinetic property in certain cases. Except for Pseudoginsenoside Rt5, none of the ligands analyzed in the ADMET study were identified as P-glycoprotein (P-gp) substrates. This characteristic offers a potential advantage by reducing the risk of drug resistance and minimizing premature elimination from the body [42]. Cytochrome P450 (CYP) enzymes play a crucial role in drug biotransformation and are key components of drug metabolism. Among these enzyme subtypes, CYP1A2, CYP2C19, and CYP2C9 are particularly important in the metabolism of various pharmaceutical compounds [16]. Therefore, the inhibitory properties of compounds on CYP enzymes vary. When examining the results in Table 2, it is observed that natural ginsenosides do not exhibit CYP1A2 inhibition. This finding suggests that they will not directly interact with other drugs metabolized by this enzyme. Compared to synthetic ligands, ginsenosides demonstrate CYP2C19 inhibition properties. The CYP2C19 enzyme plays a crucial role in the metabolism of various drugs, including antidepressants. Therefore, the potential to slow down the metabolism of drugs such as antidepressants should be considered when co-administered with compounds metabolized by CYP2C19 [40]. However, taking ginsenosides with drugs metabolized by CYP2C19 that have low bioavailability and do not cause toxicity may enhance their bioavailability. The CYP2C9 enzyme is involved in the metabolism of many drugs, such as blood thinners. As with other enzyme types, the absence of inhibition of this enzyme by ginsenosides reduces the risk of toxicity [43]. In summary, ADMET analysis is a critical component in the identification of potential pharmaceutical agents. The results of this study indicate that ginsenosides exhibit favorable pharmacokinetic profiles for the breast cancer-associated BARD1 protein, owing to their moderate absorption, selective blood–brain barrier permeability, and low interaction with CYP1A2. These findings suggest that ginsenosides may serve as promising natural alternatives to conventional chemotherapeutic agents, which are often associated with severe side effects. Furthermore, the results provide supportive evidence for the advancement of in vivo and clinical studies focusing on ginsenosides as therapeutic candidates in BARD1-targeted breast cancer treatment

F. Comparison Between Traditional Docking and AI-Based Predictions

The traditional molecular docking and AI-based binding score estimations conducted in our study reveal notable differences, particularly for ligands with complex chemical structures such as ginsenosides. For instance, Ginsenoside Ro, which exhibited a favorable binding score, was calculated as -9.5 kcal/mol using the traditional docking method, whereas the ANN-based model estimated it at -8.5408 kcal/mol. This difference can be attributed to the AI model's ability to holistically evaluate subtle fluctuations in electrostatic and conformational distributions, in contrast to the static nature of classical scoring functions [44]. In addition, Carboplatin exhibited an unstable binding performance with a score of -4.6 kcal/mol using the traditional docking method. However, the AI-based calculation estimated this value as -9.8218 kcal/mol, indicating that AI models are significantly more effective in capturing coordinative interactions often overlooked by conventional techniques. The observation that AI models can successfully characterize the subtle physicochemical properties of receptor–ligand complexes, as demonstrated in the study by Jimenez-Luna et al., is consistent with the findings of our research [29]. Another notable result in our findings pertains to the Ixabepilone complex. While the binding score obtained from classical docking was -8.0 kcal/mol, the AI-based docking model estimated a score of -6.9089 kcal/mol. This discrepancy is thought to arise from the AI model's limited ability to fully capture the structural complexity of certain drugs with macrocyclic architectures [32]. Comparing the binding score results obtained from two different techniques becomes more biologically meaningful and reliable when supported by AI-based optimization. This hybrid methodology yields more accurate and biologically relevant binding affinities for structurally diverse compounds, particularly natural ginsenosides, which are characterized by extensive hydrogen bonding capacity, flexible glycosidic linkages, and an amphipathic molecular profile [8, 12].

TABLE II
ADMET ANALYSIS FOR LIGANDS AFTER MOLECULAR DOCKING

Name of ligands	LogS (logmol/L)	HIA absorption	BBB permeant	P-gp substrate	CYP450 1A2 inhibitor	CYP450 2C19 inhibitor	CYP450 2C9 inhibitor
Ginsenoside Rk1	-4.114	Low	No	No	No	Yes	No
Ginsenoside Rk1	-4.114	Low	No	No	No	Yes	No
Pseudoginsenoside Rt5	-3.700	Moderate	Yes	Yes	No	Yes	No
Vinaginsenoside R3	-3.425	Low	Yes	No	No	Yes	No
5-FU	-1.17	Low	Yes	No	No	No	No
Carboplatin	-0.761	Moderate	Yes	No	No	No	No
Docetaxel	-4.289	Moderate	Yes	No	No	No	No
Ixabepilone	-4.964	Moderate	Yes	No	No	No	No

V.CONCLUSION

Ginsenosides obtained from the *Panax ginseng* plant were identified as potent drug candidates targeting the BARD1 gene, which is associated with breast cancer, through docking and ADMET analyses using both traditional and artificial intelligence-based models. Our findings showed that natural agents such as Ginsenoside Ro and Rk1 exhibit strong binding affinity and stable complex formation with the BARD1 protein. In addition, ADMET analyses revealed pharmacokinetic properties such as selective blood-brain barrier permeability, moderate absorption, and low toxicity. Our results were compared with synthetic chemotherapeutic agents that are widely used in the literature and preferred as control ligands. Among the synthetic agents, Carboplatin exhibited the highest binding energy according to the artificial intelligence-based model, while Docetaxel demonstrated the best binding score in classical molecular docking analysis. However, the ginsenoside Ro and Rk1 ligands stand out due to their balanced profiles in terms of both binding performance and pharmacokinetic suitability. The importance of this study lies in its combination of traditional molecular docking techniques and ANN-based binding score optimization methodology to overcome the limitations encountered in analyzing flexible and complex natural compounds such as ginsenosides, thereby providing more accurate and reliable binding score predictions. In addition, our study is one of the first to investigate the anticancer effects of ginsenosides on the BARD1 protein using a hybrid methodology that incorporates molecular docking and an ANN-based model. In this respect, it provides a significant methodological contribution to the literature by examining the therapeutic efficacy of natural ginsenosides against breast cancer-related target proteins using ANN-based, artificial intelligence-supported approaches. Our findings offer an important framework for investigating these natural agents as alternative anticancer candidates in drug discovery and development studies.

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