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Breast Cancer Therapy

RESEARCH ARTICLE

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Breast Cancer Therapy: Network Pharmacology of Several New Dithiocarbamate Complexes to Reveal Significant Target Proteins

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Abstract

Purpose: This study aims to identify key molecular targets and pathways of newly designed metal–dithiocarbamate peptide complexes in breast cancer using a network pharmacology approach, addressing the limited understanding of their systems-level mechanisms of action. **Methods:** Fifteen essential metal dithiocarbamate complexes were evaluated using ADMET profiling and network pharmacology analysis. Potential protein targets were predicted using the SwissTargetPrediction and SuperPred databases, followed by protein–protein interaction (PPI) analysis via STRING and topological analysis using Cytoscape. **Results:** A total of 502 potential targets were identified, of which 21 hub proteins were extracted through network clustering. Topological analysis revealed CDK1, CCNA2, CCNB1, and CCNB2 as key hub genes with the highest degree (≥20), betweenness, and closeness centrality values. KEGG enrichment analysis indicated that these targets were primarily involved in cell cycle regulation, cellular senescence, and p53 signaling pathway. **Conclusion:** This study provides a system-level perspective on the potential anticancer mechanisms of metal–dithiocarbamate complexes in breast cancer. Although the findings are predictive and computational, they highlight promising molecular targets that warrant further experimental validation.

Keywords: network pharmacology- dithiocarbamate- breast cancer- target proteins

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Introduction

Although there have been several advances in cancer therapy methods, cancer is still the top cause of death globally. In 2020, there were 396,914 new cases with a mortality rate of 234,511 deaths in Indonesia. One of the highest cases in Indonesia was breast cancer at 65,858/135,805,760 inhabitants, with a mortality average of 22,430/135,805,760 inhabitants. The new cases and deaths are predicted to continue to rise in the following decades [1]. The predominant treatments for breast cancer include chemotherapy, surgery, radiation therapy, endocrine therapy, and targeted therapy. Over the years, chemotherapy has led to the trend of cancer medication outperforming other types of cancer medical treatments. However, chemotherapeutic drugs present some drawbacks that cause drugs to attack not only cancer cells but also normal/healthy cells (e.g., intestinal

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epithelium) [2]. Moreover, cancerous cells are not completely targeted, producing more virulent cancer. This lack of specificity emerges in severe side effects, including cardiotoxicity, diarrhea, pain, nausea, hair loss, dry skin, and immune system depression [3-5]. Years later, targeted therapies offer a new medication that targets only cancer cells [6]. This new generation of therapies has garnered significant attention, especially from researchers and The Cancer Genome Atlas (NCI/NIH) [7].

Targeted therapy selection is based on the type of breast cancer and phase at diagnosis [8]. Several primary types of breast cancer include hormone receptor (HR) positive/ human epidermal growth factor receptor 2 (HER2) negative, HR positive/HER2 positive, HR negative/HER2 negative, and HR negative/HER2 positive [9]. Up to date, the U.S. Food and Drug Administration (FDA) has approved over 20 targeted cancer therapies from various groups of cancer [10]. Targeted therapy utilizes drugs or other substances to block a specific pathway responsible for increasing breast cancer growth and survival. This treatment has many benefits, such as fewer side effects, more efficacious, and less damaging to healthy tissue and cells than conventional therapeutic methods [6].

Small molecule inhibitors/drugs are one of the main types of targeted cancer therapies. These drugs work by inhibiting the specific enzyme and growth factor receptors involved in the proliferation of cancer cells, such as EGFR (Epidermal Growth Factor Receptor) [6]. The commonly used clinical treatment for HER2 receptor is Herceptin/ Trastuzumab, which has been approved for breast cancer medication [11]. The drug acts by inhibiting the effects of HER2+ and triggering the body's immune system to destroy and eliminate cancer cells [12]. However, there are side effects of Herceptin, including skin rashes, nausea, fatigue, and cardiac dysfunction [13]. Hence, other targeted drugs should be investigated to obtain more efficacious therapeutic medicines for some breast cancer targets.

In recent years, the synthesis strategy of metal complexes has intrigued researchers to create novel therapeutic compounds. Metal-based drugs offer promising benefits such as anticancer, antimalarial, antibacterial, and antioxidant activity. These anticancer drugs provide lower side effects than conventional platinum-based drugs. Selecting a ligand is a pivotal process in drug discovery to increase the biological activity of complex compounds. Dithiocarbamate, a chelating metal agent, has been widely used in medicine. The unique feature of dithiocarbamate and its derivatives provides some advantages. Irfandi et al., have successfully examined several essential metal dithiocarbamate complexes as cancer drugs through experimental and computational studies [14-18]. Unfortunately, although comprehensive studies have been conducted on synthesizing dithiocarbamate complexes and examining them through in vitro, in vivo, and computational studies, it is not fully understood what are the specific targets and how the mechanism of action of the complexes is in the treatment of breast cancer.

Meanwhile, studies on pathway prediction or network pharmacology analysis offer a strategy to predict unknown targets and pathways of drug candidates. Network pharmacology integrates diverse disciplines of pharmacology, systems biology, data informatics, and other related fields [19-21]. In recent years, this study has been utilized to unravel the unknown target and mechanism of the action of potential drugs. Qin et al. investigated the mechanism of action of herbal medicine to treat chronic kidney disease using a network pharmacological study [22]. They revealed that the result from the computational simulation is straightforward for experimental validation. Si Tang et al. employed network pharmacology and molecular docking to explore the pharmacodynamic substances and mechanism of "Mung Bean" against bacterial infection [23]. Another, Zahoranszky-Kohalmi, G. et al., developed SmartGraph-network pharmacology to integrate high-quality bioactivity data and biological pathways [24]. These examples show that network pharmacology offers a valuable tool to identify targets and pathways of drug candidates.

Therefore, this study will utilize a target identification approach to unravel the target and mechanism of action through network pharmacology, which is one of the approach to prove the hypothesis and the theoretical aspect in . In drug discovery, target identification is the key to determining the drug mechanism of action and side effects [25]. Lack of knowledge of the drug mechanism of action is one of the main causes of potential drug candidates failing in clinical trials. Understanding the drug target and its mechanism of action can minimize the drug's lack of efficacy and the occurrence of off-target effects, which often cause drug side effects [26]. In addition, we employed ADMET analysis to investigate the pharmacokinetic properties of potential oral drugs. ADMET identification includes the drugs' absorption, distribution, metabolism, excretion, and toxicology. This analysis is widely used to understand drug discovery and development [27], and to provide a fast and preliminary screening before in vitro analysis [28], which become one of the most essential parts of computational drug design [29]. By combining ADMET analysis and network pharmacology, this study is expected to elucidate the specific therapeutic targets and involved pathways of new dithiocarbamate complexes treating breast cancer better to understand the mechanism of action and clinical application.

Despite extensive experimental and computational studies on metal-based dithiocarbamate complexes, most investigations have focused on cytotoxicity evaluation or molecular docking against single protein targets. The systems-level mechanisms, including how these complexes simultaneously interact with multiple proteins and pathways relevant to breast cancer progression, remain poorly understood. This represents a critical knowledge gap, particularly given the multi-target nature of metal-based therapeutics. Unlike previous studies, the present work applies an integrated network pharmacology framework to newly designed metal–dithiocarbamate peptide complexes, combining multi-database target prediction, protein–protein interaction analysis, and pathway enrichment. This approach enables the identification of key hub genes and signaling pathways at a systems biology level, providing novel insights into

the potential mechanisms of action of these complexes beyond conventional single-target analyses.

Materials and Methods

The research flow diagram explains the data, database, and programs used and can be seen in Figure 1.

Calculation and prediction of physicochemical, drug-likeness, absorption, and distribution of the compounds

A total of 15 dithiocarbamate metal complex compounds have been designed manually as shown in Figure 2. The SMILES format of the compounds was used to calculate and predict physicochemical, drug-likeness, absorption, and distribution with the SwissADME (http://swissadme.ch/) (Daina et al. [31]) and admetSAR 2.0 (Yang et al. [27]). Lipinski's rule of five is a parameter used to predict physicochemical and drug-likeness, which consists of a molecular mass of less than 500 Dalton, mLogP of less than 5, hydrogen bond donors of less than 5, hydrogen bond acceptors of less than 10, and molar refractivity between 40-130 (Ghose filter) (Sen et al., 2021). Calculation and prediction of absorption and distribution of the compounds consisting of human intestinal absorption (HIA), human oral bioavailability (HOB), caco-2 permeability, and blood-placenta barrier (BPB).

Frontier molecular orbital diagrams, the highest occupied molecular orbitals (HOMO) and lowest unoccupied molecular orbitals (LUMO) in the 15 studied dithiocarbamate complexes, are calculated and represented in Figure 2. According to Figure 2, two electrons are in the HOMO and are mainly localized in brown and blue. As for LUMO, if the molecule accepts electrons, these electrons will be localized to the brown and blue zones.

For researchers, the study of anticancer agents is crucial. Both experimental and computational methods can be used to conduct this type of inquiry. Anticancer characteristics are defined in computational chemistry using some of the specific parameters provided in the computational breakdown. EHOMO is the initial input parameter. The molecule can readily donate electrons to an appropriate acceptor structure if the EHOMO is high. These findings show that as EHOMO rises, biological activity does as well [30]. According to EHOMO, the ordering of biological activity progressively is Zn(II) arginine-cysteine-Dithiocarbamate > Co(II)arginine-cysteine-dithiocarbamate > Mn(II)arginine-cysteine-dithiocarbamate > Co(II)-proline-cysteine-dithiocarbamate > Cu(II)arginine-cysteine-dithiocarbamate. ELUMO serves as the second parameter. The molecule can take electrons from the matching molecule if the value is low; this finding shows that activity rises as ELUMO falls. Ni(II)proline-cysteine-dithiocarbamate is ranked above Zn(II)proline-cysteine-dithiocarbamate, Zn(II)proline-cysteine-proline-dithiocarbamate, and Co(II)proline-cysteine-proline-dithiocarbamate in the order of biological activity. The energy difference between LUMO and HOMO is the third factor. The degree of electron freedom affects biological reactivity. The mentioned activity rises when EGAP values fall. Mn(II)proline-cysteine-dithiocarbamate is ranked first in the se activity hierarchy, followed by Zn(II)arginine-cysteine-dithiocarbamate, Ni(II)proline-cysteine-proline-dithiocarbamate, and then Cu(II)arginine-cysteine-dithiocarbamate. Hardness and softness of chemicals make up the fourth parameter. With the HSAB (hard-soft-acid-base) approach, the trend of molecular coordination towards a suitable structure can be

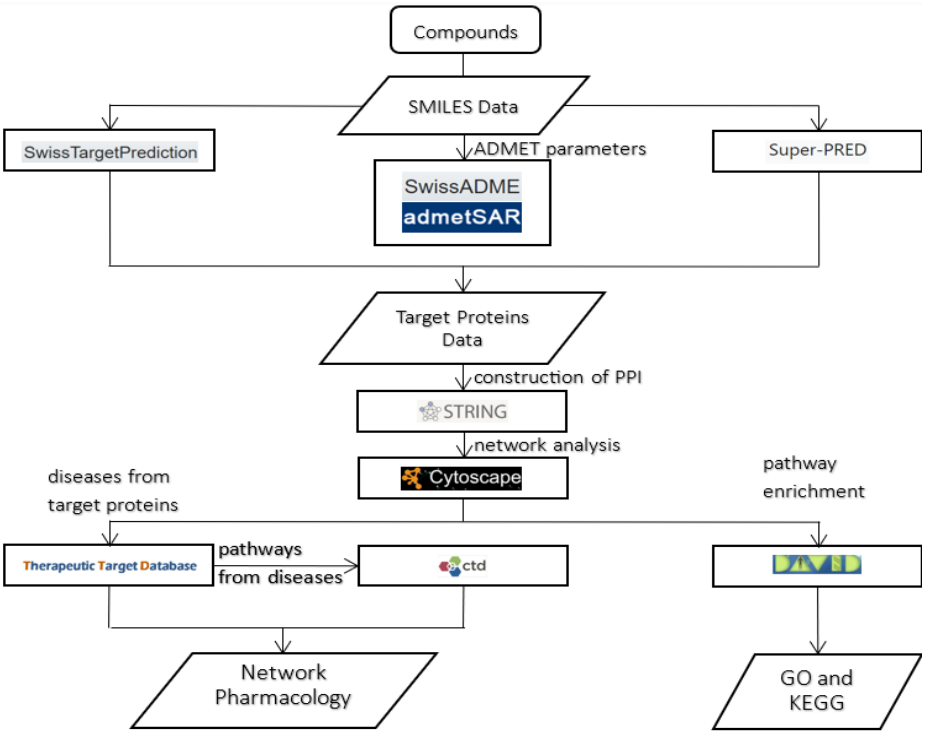

Figure 1. The Research Flow Diagram Explains the Data, Database, and Programs Used

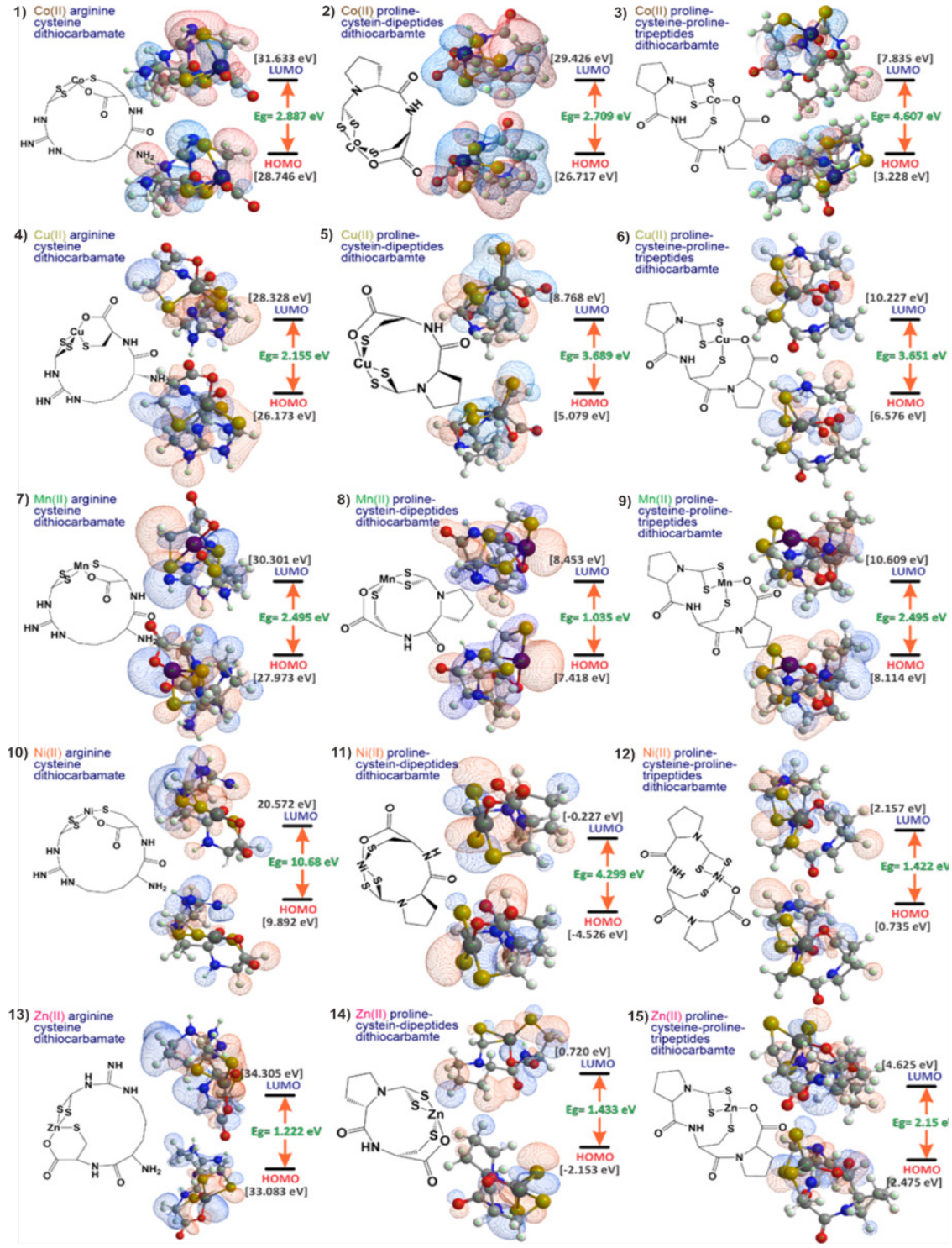

Figure 2. Structure Design and Frontier Molecular Orbital Diagrams of 15 Essential Metal Dithiocarbamate Complex

addressed. Hard acids tend to coordinate with hard bases, and soft acids prefer to coordinate with soft bases. The EGAP of soft molecules is minimal, whereas the EGAP of hard molecules is substantial. Soft nature. Cells, enzymes, and other biological structures. As a result, soft molecules have higher biological activity than hard molecules. Mn(II)proline-cysteine-dithiocarbamate is ranked first, followed by Zn(II)arginine-cysteine-dithiocarbamate, Ni(II)proline-cysteine-proline-dithiocarbamate, and then Cu(II)arginine-cysteine-dithiocarbamate.

Complexation improves anticancer activity, as determined by the ranking above. The anticancer activity of the complexes Mn(II)proline-cysteine-dithiocarbamate, Ni(II)proline-cysteine-dithiocarbamate, and Zn(II) arginine-cysteine-dithiocarbamate is greater than that of the other complexes. Based on EHOMO parameters, ELUMO, EGAP between LUMO and HOMO, and HSAB properties, it is clear from the ranking above that the Mn(II)proline-cysteine-dithiocarbamate, Ni(II)proline-cysteine-dithiocarbamate, and Zn(II)arginine-cysteine-dithiocarbamate complexes may be good candidates for cancer.

Screening targets of the compounds and constructing the protein-protein interaction network

The targets of the compounds were obtained from Swiss Target Protein (http://swisstargetprediction.ch/) [31, 32] and SuperPred databases (https://prediction.charite.de/) to get possible predictions of potential targets [33]. The results of the target screening were then searched for potential interactions using STRING (http://string-db.org) [34] with high confidence of 0.700 for the required score. The results obtained from STRING were then analyzed using Cytoscape v3.8.2 software (https://cytoscape.org/) [35] and clustered with MCODE [36] tools to obtain sub-networks.

Screening diseases activities of the targets

Therapeutic Target Database (https://db.idrblab.net/ttd/) [37] was used to search for diseases associated with target proteins. The target diseases were then used to build a network between the target and the disease.

Screening pathways of the disease

Diseases obtained from the Therapeutic Target Database website were then submitted to the Comparative Toxicogenomics Database (http://ctdbase.org/) [38] to predict the associated KEGG pathway (https://www.kegg.jp/) [39]. The KEGG pathways obtained were used to create a network.

Network construction of compound-target-disease-pathway

The network was built with several models, namely multi-component (compound)--multi-target, multi-target--multi-disease, multi-disease--multi-pathway, and multi-target--multi-pathway which were then combined into multi-component--target--disease--pathway. The network was built using Cytoscape v3.8.2 software.

Pathway enrichment analysis

Integrated Discovery and Annotation Database (https://david.ncifcrf.gov/tools.jsp) [40] is a tool to look for probable pathway enrichment of the target protein using the Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) databases, with a cut-off of p-value 0.01. The biological procedures, cellular elements, and molecular operations that make up GO are used to identify it. The top ten GO and KEGG pathways were then represented using SRPlot (http://www.bioinformatics.com.cn/).

Topological analysis of protein-protein interaction networks

Most biological networks represents scale-free [41] model topology where the number of connections for each node follows a power law distribution. This feature of topological characteristics of biological networks is strongly related to the stability [42] and the sustainability of networks [43, 44], as well as its role in cell survival [45]. In this study, we investigated the centrality measures [46, 47] to understand protein-protein interaction structural characteristics. The centrality measures we considered in this work are as follows.

• Degree of a node denotes the number of edges upon protein that is linked with it in a network [48].

• Betweenness of a node denotes the ability of protein to control communication between proteins through the shortest paths [49].

• Closeness of a node denotes the reciprocal of the average distance from a node to another nodes [50].

All computational analyses were performed using publicly available databases and software with default parameters unless otherwise stated. SwissTargetPrediction (version 2019) and SuperPred (accessed in 2024) were used to predict potential protein targets based on SMILES structures, with Homo sapiens selected as the target organism. Duplicate targets from both databases were merged and non-human proteins were excluded. Protein–protein interaction (PPI) analysis was conducted using the STRING database (version 11.5) with a minimum required interaction score of 0.700 (high confidence). Network construction and topological analysis were performed using Cytoscape software (version 3.8.2). Hub proteins were identified based on Degree, Betweenness Centrality, and Closeness Centrality measures. Clustering analysis was conducted using the MCODE plugin with default parameters (degree cutoff = 2, node score cutoff = 0.2). Pathway enrichment analysis was performed using the DAVID database (version 2021) with a significance threshold of $p < 0.01$. Only pathways related to cancer and cell cycle regulation were prioritized for biological interpretation.

Results

Compounds physicochemical, drug-likeness, absorption, and distribution

This study made predictions for 15 compounds based on Lipinski's rule of five. Lipinski's rule of five consists of a molecular weight (MW) of less than 500 Dalton, mLogP of less than 5, hydrogen bond acceptors of less than 10, hydrogen bond donors of less than 5, and molar refractivity between 40-130 (Ghose filter) (Sen et al., 2021). The prediction results using the SwissADME website show that all compounds fulfill Lipinski's rule of five. Screening of absorption and distribution of compounds using admetSAR showed that all compounds could not pass through the blood-brain barrier penetration and caco-2 permeability, ten compounds could be absorbed by the human intestine, and five compounds could be absorbed orally. Ni(II)proline-cysteine-dithiocarbamate is the only compound that meets the requirements of human intestinal absorption (HIA) and human oral bioavailability (HOB) (Table 1). Absorption, distribution, metabolism, excretion, and toxicity (ADMET) of the compounds is essential parameters in determining drug candidates (Guan et al. [27]).

The ADMET analysis provides an initial assessment of the pharmacokinetic suitability of the investigated compounds. Compliance with Lipinski's rule of five indicates favorable drug-likeness, while positive human intestinal absorption (HIA) and human oral bioavailability (HOB) suggest potential oral administration. In contrast, predicted blood–brain barrier (BBB) non-penetration may indicate reduced risk of central nervous system toxicity.

Table 1. Physicochemical, Drug-Likeness, Absorption, and Distribution of the Compounds Using SwissADME and admetSAR Databases

No	Compound name	MW (<500 D)	MLogP (<5)	H-bond acceptors (<10)	H-bond donors (<5)	Molar refractivity (40-130)	Lipinski	BBB	HIA	Caco-2	HOB
1	Co(II) arginine cysteine dithiocarbamate	410.4	-1.35	5	5	96.66	Yes	-	-	-	-
2	Co(II) proline cysteine dipeptides dithiocarbamate	351.33	-0.38	4	1	76.82	Yes	-	+	-	-
3	Co(II) proline cysteine proline tripeptides dithiocarbamate	448.45	-0.27	5	1	105.75	Yes	-	+	-	-
4	Cu(II) arginine cysteine dithiocarbamate	415.01	-1.35	5	5	96.66	Yes	-	-	-	+
5	Cu(II) proline cysteine dipeptides dithiocarbamate	355.94	-0.38	4	1	76.82	Yes	-	+	-	-
6	Cu(II) proline cysteine proline tripeptides dithiocarbamate	453.06	-0.27	5	1	105.75	Yes	-	+	-	-
7	Mn(II) arginine cysteine dithiocarbamate	406.41	-1.35	5	5	96.66	Yes	-	-	-	+
8	Mn(II) proline cysteine dipeptides dithiocarbamate	347.34	-0.38	4	1	76.82	Yes	-	+	-	-
9	Mn(II) proline cysteine proline tripeptides dithiocarbamate	444.45	-0.27	5	1	105.75	Yes	-	+	-	-
10	Ni(II) arginine cysteine dithiocarbamate	410.16	-1.35	5	5	96.66	Yes	-	-	-	+
11	Ni(II) proline cysteine dipeptides dithiocarbamate	351.09	-0.38	4	1	76.82	Yes	-	+	-	+
12	Ni(II) proline cysteine proline tripeptides dithiocarbamate	448.21	-0.27	5	1	105.75	Yes	-	+	-	-
13	Zn(II) arginine cysteine dithiocarbamate	416.85	-1.35	5	5	96.66	Yes	-	-	-	+
14	Zn(II) proline cysteine dipeptides dithiocarbamate	357.78	-0.38	4	1	76.82	Yes	-	+	-	-
15	Zn(II) proline cysteine proline tripeptides dithiocarbamate	454.89	-0.27	5	1	105.75	Yes	-	+	-	-

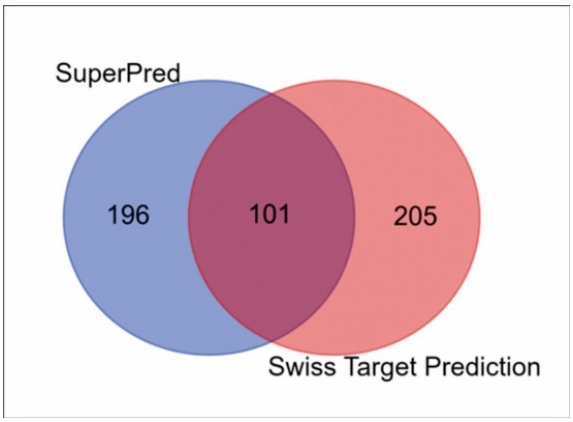

Figure 3. Total of the Target Protein Result of Screening Using Swiss Target Prediction and SuperPred Databases

Table 2. Analysis Results of Sub-Network with 21 Targets Arranged by Highest Betweenness Centrality with Degree, and Closeness Centrality Values

No.	Gene Name	Betweenness Centrality	Degree	Closeness Centrality
1	*CDK1*	0.041059087	20	1
2	*CCNA2*	0.041059087	20	1
3	*CCNB2*	0.041059087	20	1
4	*CCNB1*	0.041059087	20	1
5	*CDC25C*	0.034995823	19	0.952
6	*KIF11*	0.017191084	16	0.833
7	*CDC25B*	0.015223475	15	0.800
8	*CHEK1*	0.01371364	16	0.833
9	*CDK2*	0.010883459	14	0.769
10	*AURKA*	0.009876965	15	0.800
11	*CCNE1*	0.003778195	12	0.714
12	*AURKB*	0.003694843	14	0.769
13	*MELK*	0.003694843	14	0.769
14	*TYMS*	0.003011696	12	0.714
15	*CCNE2*	0.002792398	12	0.714
16	*CCNA1*	0.002792398	12	0.714
17	*WEE1*	0.001754386	11	0.690
18	*PBK*	9.17E-04	13	0.741
19	*TOP2A*	9.17E-04	13	0.741
20	*CDK4*	0	10	0.667
21	*NEK2*	0	12	0.714

Protein-protein interaction network

As shown in Figure 3, the integration of two independent target prediction SwissTargetPrediction and SuperPred resulted in a total of 502 predicted target proteins. Among these, 101 overlapping targets were identified by both tools, suggesting a higher level of confidence compared to targets predicted by a single platform. This dual-platform strategy was intentionally applied to reduce false-positive predictions and to enhance the robustness of target identification. The overlapping proteins were therefore considered as priority candidates for subsequent protein–protein interaction (PPI) analysis

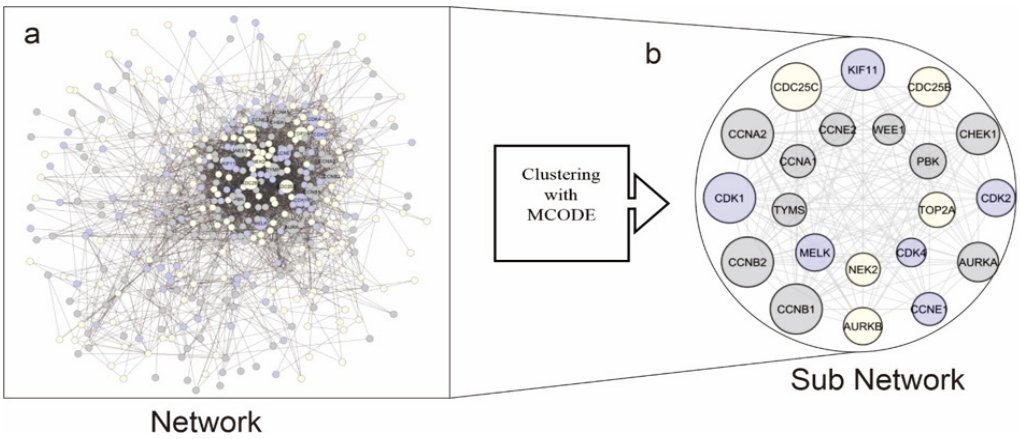

Figure 4. Illustration of Protein-Protein Interaction (a) network and (b) sub-network: the gray nodes (protein from Swiss Target Prediction), the cream nodes (protein from SuperPred), and the purple nodes (overlap protein)

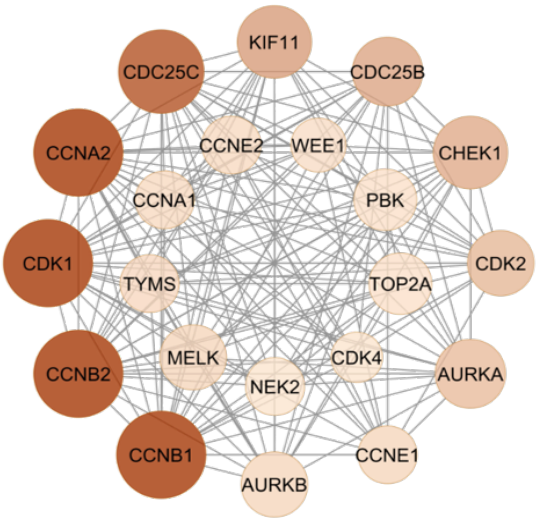

Figure 5. Topological Properties of the Sub-Network, the Color Intensity of Nodes Corresponds to Betweenness Centrality Values, and the Size of Nodes Corresponds to Degree Values

and network topology evaluation. The target proteins obtained were then submitted to STRING to obtain interactions between proteins with a minimum confidence score of 0.700. The results of protein interactions were then analyzed using Cytoscape, which showed that there were 437 target proteins with 2540 interactions. The results of screening target compounds using the Swiss Target Protein and SuperPred databases showed that five compounds had the most interactions or pathways with protein targets, namely Co(II) arginine cysteine Dithiocarbamate, Cu(II) arginine cysteine Dithiocarbamate, Mn(II) arginine cysteine Dithiocarbamate, Ni(II) arginine cysteine Dithiocarbamate, and Zn(II) arginine cysteine Dithiocarbamate (Figure 4a, Supplementary Table 1). Figure 4a shows that protein-protein interaction networks tend to be dense with a scale-free model in which link distribution to nodes follows a power law distribution. This describes the presence of the large hubs of the important nodes, usually, while the others have small links or connections. Then, the selection of potential protein

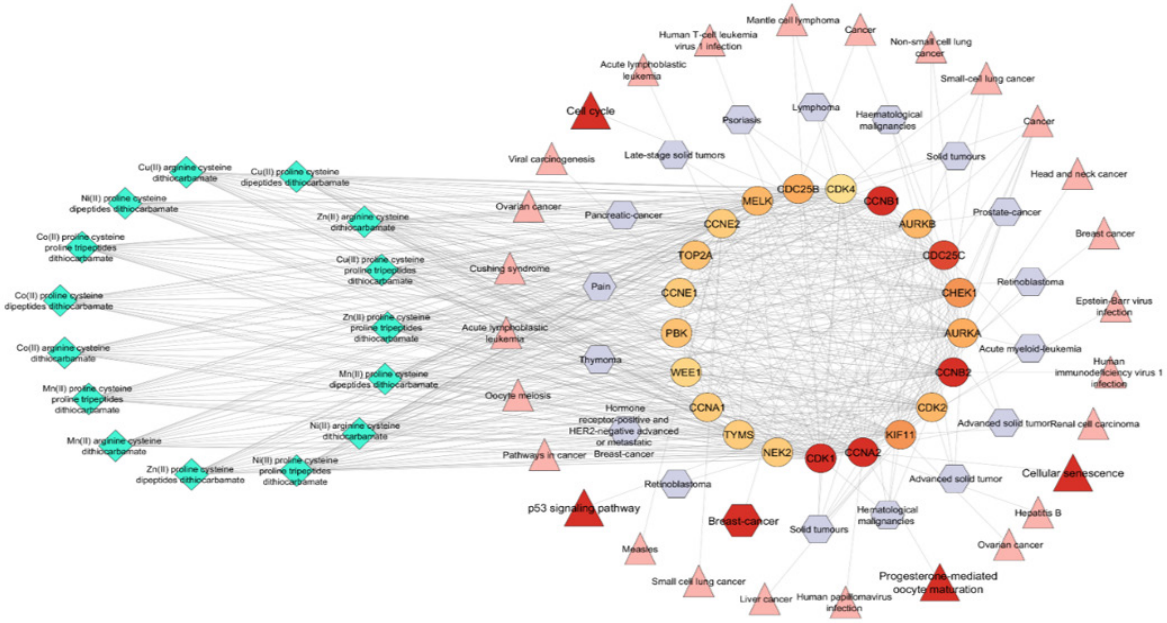

Figure 6. Network Pharmacology of Multi-Components--Targets--Diseases--Pathways. The diamond, triangle, hexagon, and ellipse nodes represent compounds, pathways, diseases, and proteins.

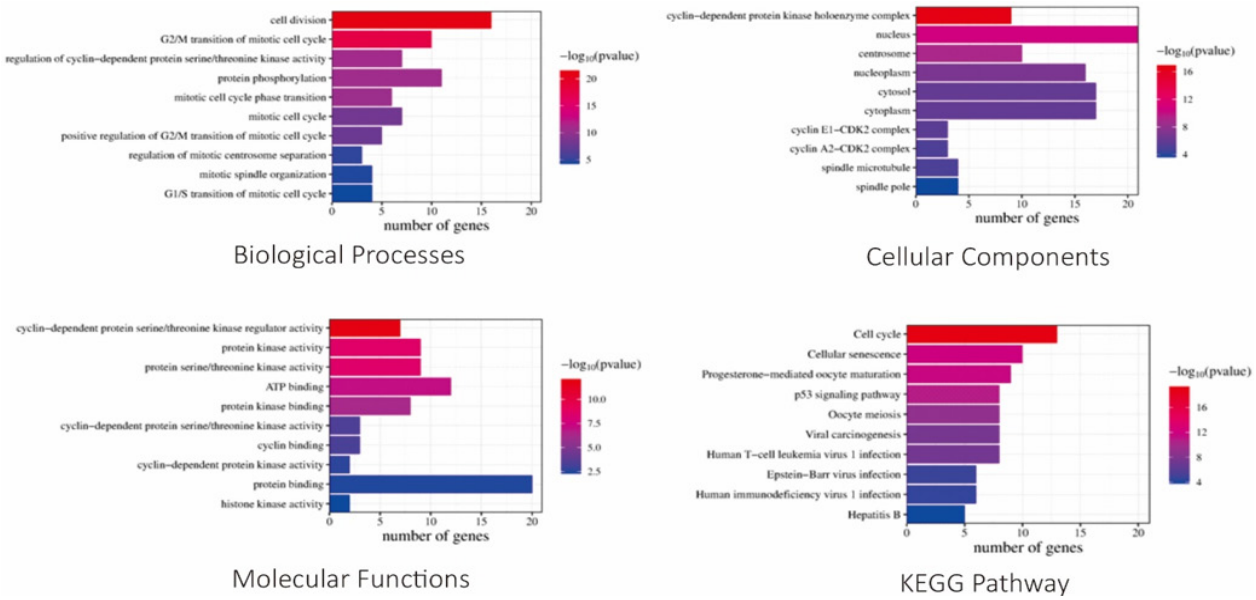

Figure 7. The Top 10 GO and KEGG Pathway of Target Proteins

targets was carried out by clustering using MCODE tool, and 21 potential targets were found with 155 interactions (Figure 4b). It shows 16 proteins from Swiss Target Prediction, 11 proteins from SuperPred, and six overlap proteins from both. Note that those 21 potential targets in the hub nodes are located close together and have quite a lot of interactions compared to the other nodes outside the hub area. In addition, the calculation of Betweenness Centrality, Degree, and Closeness Centrality was also performed for the selected target proteins (Table 2, Figure 5).

In the PPI network visualization (Figure 4), nodes represent target proteins, while edges represent protein–protein interactions. The color of the nodes indicates the origin of the predicted targets: gray nodes represent proteins predicted by SwissTargetPrediction, cream-colored nodes represent proteins predicted by SuperPred, and purple nodes indicate overlapping targets identified by both platforms. Node size corresponds to the degree value, reflecting the number of interactions

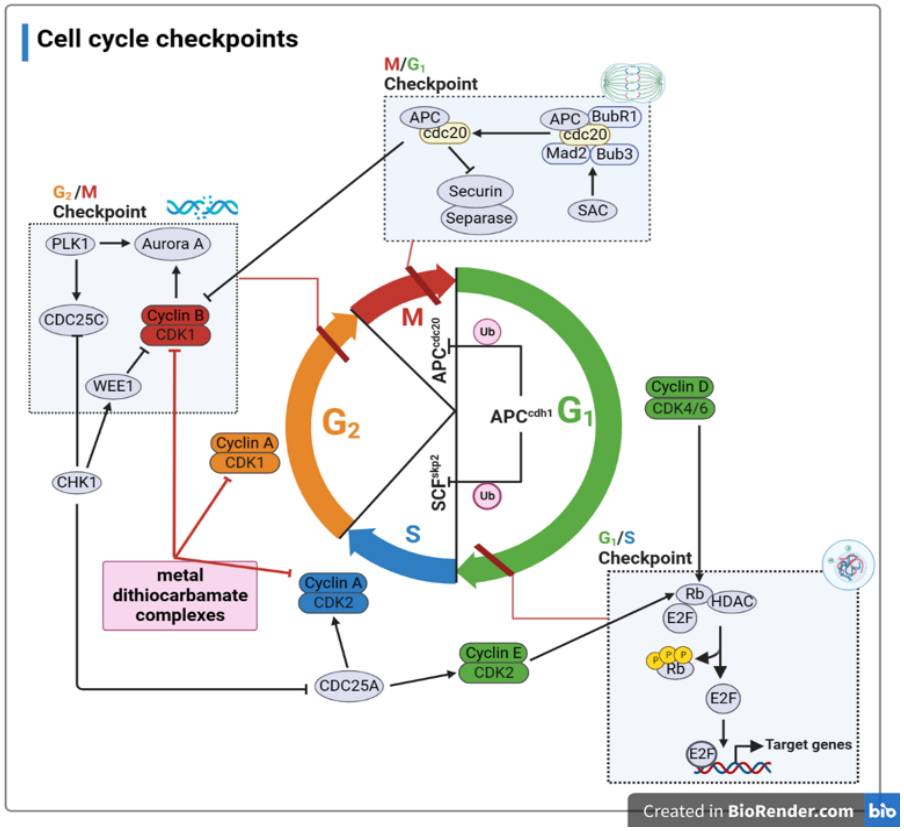

Figure 8. The Regulatory Mechanism of Cell Cycle Progression. The cell cycle consists of G1, S, G2, and M phases. Cyclin A is defined as CCNA-1/-2/-3, while cyclin B is CCNB-1/-2/-3.

associated with each protein, whereas edge density reflects the overall connectivity of the network. Proteins with larger node sizes are considered hub proteins, suggesting a more central regulatory role within the biological network.

To better understand the functional relationships among the predicted targets, the overlapping and non-overlapping proteins were further analyzed using a protein–protein interaction (PPI) network approach. STRING database analysis with a high-confidence interaction threshold (score ≥ 0.700) was applied to ensure biological relevance of the interactions. The resulting network was visualized and analyzed using Cytoscape to identify highly connected nodes (hub proteins) that may play key regulatory roles in breast cancer-related signaling pathways.

As shown in Table 2, the potential target proteins resulting from clustering using MCODE are CDK1, CCNA2, CCNB2, CCNB1, CDC25C, KIF11, CDC25B, CHEK1, CDK2, AURKA, CCNE1, AURKB, MELK, TYMS, CCNE2, CCNA1, WEE1, PBK, TOP2A, CDK4, and NEK2. To enhance our understanding of its structural characteristics, we visualized them in Figure 5. It illustrates the betweenness centrality values based on the color intensity of nodes and the degree values based on the size of nodes. It is evident in visualization that CDK1, CCNA2, CCNB2, and CCNB1 interact more with other proteins than others. Thus, *CDK1, CCNA2, CCNB2,* and *CCNB1* were hub genes because they have the highest degree values. Besides, they also have the highest betweenness centrality and closeness centrality values compared to others. This suggest that *CDK1, CCNA2, CCNB2*, and *CCNB1* can be concluded as essential genes which become a key notion in systems biology [51, 52] and cancer [53, 54].

The identification of hub proteins such as CDK1, CCNA2, CCNB1, and CCNB2 is biologically significant, as these proteins are well-known regulators of cell cycle progression and mitotic control. Their high degree, betweenness centrality, and closeness centrality values indicate that they act as key regulatory nodes within the network, potentially coordinating multiple signaling pathways associated with breast cancer progression. Disruption of such hub proteins is therefore likely to exert a broader therapeutic impact compared to targeting peripheral nodes, supporting their relevance as promising targets for anticancer drug development.

Diseases and pathways of the compounds

We used The Therapeutic Target Database (TTD) to search diseases associated with the target protein. TTD is a database containing information about therapeutic proteins, nucleic acids, diseases, pathways, and drugs directed at each target (Zhou et al. [37]). The screening results with TTD showed that there were 24 diseases associated with 14 targets from the sub-network.

Network pharmacology

To observe associations between compounds, proteins, diseases, and pathways, we merged them using Cytoscape. The network shows the associations between 15 compounds, 21 proteins, 18 diseases, and 23 pathways (Figure 6). The topology of network pharmacology shows associations between compounds and cancer based on the target protein, disease, and pathway involved. Diamond-shaped nodes (green) represent metal complexes with dithiocarbamate peptide ligands, indicating that the compound interacts with a specific biological target. Elliptical nodes (yellow/red/orange) represent target proteins involved in biological pathways, with different colors likely indicating the level of importance of the interaction with a disease. Triangular nodes (red/pink) represent diseases including cancer, leukemia, psoriasis, and viral infections, indicating that the pathways affected by the compound and protein are associated with a variety of medical conditions. Hexagonal nodes (red) represent biological pathways involved in these systems.

GO and KEGG Pathway

Pathway enrichment analysis using the DAVID database with p-value <0.01 shows the association of the target proteins with 26 biological processes, 18 cellular components, 12 molecular components, and 15 KEGG pathways. The main targets *CDK1, CCNA2, CCNB2*, and *CCNB1* and neighboring genes were primarily enriched for cell division, G2/M transition of the mitotic cell cycle, and regulation of cyclin-dependent protein serine/threonine kinase activity. Cellular component annotations for these genes included cyclin-dependent protein serine/threonine kinase holoenzyme complex, nucleus, and centrosome. Enriched molecular functions included cyclin-dependent protein serine/threonine kinase regulator activity, protein kinase activity, and protein serine/threonine kinase activity. Screening pathways based on target proteins also show associations with tumor development and pathogenesis of breast cancer such as cell cycle, cellular senescence, progesterone-mediated oocyte maturation, p53 signaling pathway, and oocyte meiosis.

Discussion

Based on a computational approach, this study investigated the potential targets and key pathways of dithiocarbamate complexes toward breast cancer. In the drug discovery process, target identification is the crucial step for exploring the appropriate target and the mechanism of action of small molecules. This study utilized network pharmacology analysis to obtain the potential targets, gene ontology, and pathway of the complexes.

There are 4 top targets with higher degrees resulting from the topology analysis, namely 1) CDK1, 2) CCNA2, 3) CCNB2, and 4) CCNB1. Most of the main targets have many associations with gene ontology and KEGG pathway enrichment. The highest value of gene ontology and KEGG pathway enrichment associated with the pathology of breast cancer will be discussed.

According to Figure 7, the biological processes involve cell division, G2/M transition of the mitotic cell cycle, and regulation of cyclin-dependent protein serine/threonine kinase activity. The unlimited number of cell divisions is one of the most important properties of cancer cells, leading to immortality [55]. In the normal condition, telomers are shortened with each cell division, while in the immortal case, telomers are lengthened by

the enzyme telomerase which is expressed up to 100% in breast cancer [56]. The G2/M transition of the mitotic cell cycle is defined as the progression from G2-phase to M2-phase (mitosis). The process begins when cyclin B reaches a threshold level in the cell cycle [57, 58]. Cyclin-dependent protein serine/threonine kinases (CDKs) are key regulatory enzymes that play an important role during cell proliferation. Since the upregulation of CDKs could exacerbate cell proliferation, the dysregulation of its activity has been considered an attractive target in breast cancer therapy [59, 60]. The results align with the cellular component and molecular function profiles which involve the role of cyclin-dependent kinase activities.

Further enrichment analysis obtained the potential KEGG pathways. We found that the cell cycle is the most enriched pathway. The cell cycle is essential for cell growth. Since the abnormalities of the cell cycle lead to cancer cell formation, targeting the cell cycle has been implemented in cancer treatment [61]. The detailed mechanism of the cell cycle is shown in Figure 8. A number of cell cycle-related genes, such as *CCNB1, CCNB2, CCNA2,* and *CDK1*, which play critical roles in the onset and development of cancer, were also found in the current study. It has been established that CCNB1 is a biomarker for the prognosis of patients with ER-positive breast cancer and for assessing how well hormone therapy works [62]. According to Deng et al., CCNB1 was overexpressed in breast cancer tissues and was related to a bad prognosis for patients [63]. Additionally increased in breast cancer patients is CCNB2, or cyclin B2. According to research by Sun et al., individuals with breast cancer who had high expression levels of *CCNB2* had worse outcomes in terms of overall survival (OS), recurrence-free survival (RFS), and distant metastasis-free survival (DMFS)[64]. CCNA2, cell cycle regulator cyclin A2, is a member of the cyclin family. It regulates the transition of G1-S and G2-M in the cell cycle [65-67]. In ER+ breast cancer patients, there is a high expression of CCNA2. Therefore, knockout of the CCNA2 prevented G2-M progression, resulting in the disruption of the cell cycle and inducing cell apoptosis [63], [68]. Some inhibitors have been developed to target CDK1, one of the crucial targets of CDKs, in order to slow the growth of tumors and trigger apoptosis in triple-negative breast cancer [69]. Cancer patients with high CDK1 expression had significantly lower 5-year relapse-free survival rates than those with low CDK1 levels. [70]. These data suggest that *CCNB1, CCNB2, CCNA2,* and *CDK1* may serve as potential biomarkers for cancer therapy, especially for breast cancer medication. The results also indicate that metal dithiocarbamate complexes offer novel therapeutic agents targeting the specific biomarker of breast cancer.

As shown in Figure 8, the main targets *CCNB1, CCNB2, CCNA2*, and *CDK1* are mainly involved in the S, G2, and M phases. The cell cycle is an irreversible process that maintains a sequential step regulated by three key checkpoints: G1 checkpoint (restriction checkpoint), G2/M checkpoint, and M/G checkpoint (spindle checkpoint). Those checkpoints are required to prevent mutant cells from replicating in the cell cycle. The problem in the checkpoints causes proliferation of mutant cells, leading to cancer. Cyclin-dependent kinases especially CDK1, 2, 4, 6 are crucial for the progression of the cell cycle which is a process severely disrupted in cancer cells [71–75]. CDK activation is dependent on the synthesis and degradation of regulatory cyclins and key cell cycle regulators APC/C and SCF E3 ligase complexes [76].

Growth factors commence the G1 phase by activating cyclins D1, D2, and D3, which interact with CDK4 or CDK6. In this phase, cyclin D-CDK4/6 phosphorylates Rb protein to trigger E2F releasing from the Rb-E2F complex, leading to inactivation of the restriction of G1 checkpoint. Cyclin E-CDK2 also phosphorylates Rb protein to enable the transcription of genes required for entrance into S phase. The progression in S is driven by cyclin A-CDK2. In S phase, after DNA replication finished, cells in G2 phase will pass through the G2/M checkpoint. Following this, in G2 phase, it is controlled by cyclin A-CDK1, while the progression from late G2 to the end of mitosis are regulated by cyclin B-CDK1 [71, 73]. The process of mitosis, chromosomal segregation, and cytokinesis also requires other kinases, such as PLK1 (Polo-like Kinase 1) and Aurora A/B [75]. APCcdc20 controls the spindle assembly checkpoint during mitosis. Additionally, it is in charge of the degradation of cyclin B to activate CDK1 and the activation of Separase and Securin, respectively. APCcdh1 controls the ubiquitination and protein stability of Cdc20 and SKP2 to guarantee the orderly activation and deactivation of APC/C and SCF during cell cycle phases [76]. Cell cycle progression is carefully regulated by cyclin-CDK activators and inhibitors that either destroy cyclins or stop cyclin-CDK activation. Due to the inactivation or mutation of suppressor genes, which results in the overexpression of cyclins-CDKs and the uncontrolled advancement of the cell cycle and mitosis in cancerous conditions, cells lose many inhibitory regulators [77].

Previous studies on metal-based dithiocarbamate complexes have primarily emphasized cytotoxicity assays and single-target molecular docking analyses. In contrast, the present study extends these findings by demonstrating that such complexes may exert anticancer effects through coordinated modulation of multiple cell cycle–related proteins, particularly CDK1, CCNA2, CCNB1, and CCNB2. This multi-target perspective aligns with emerging evidence that effective cancer therapeutics often act on interconnected signaling networks rather than isolated molecular targets.

Nevertheless, this study has several limitations. All findings are based on in silico predictions and network topology analysis, without experimental validation. While network pharmacology provides valuable systems-level insights, experimental approaches such as molecular docking, in vitro assays, and in vivo models are required to confirm the predicted compound–target interactions and biological effects. These validations are planned for future work.

While our work is computational and theoretical, it highlights the essential role of certain genes in cancer development. This study demonstrates that network pharmacology enables a systems-level understanding of drug-target interactions within complex biological

networks. Unlike conventional single-target drug discovery, network pharmacology accounts for the interconnected nature of signaling pathways, gene regulatory networks, and protein interactions, which are often disrupted in cancer. Additionally, it facilitates the identification of key driver genes, potential druggable targets, and synergistic drug combinations, ultimately enhancing precision medicine approaches for cancer treatment. Despite these valuable insights, translating predictions into molecular modeling studies such as docking and molecular dynamics (MD) simulations remains a time-intensive process. Molecular docking requires extensive optimization of ligand and protein structures, along with multiple docking runs to ensure accuracy. Likewise, MD simulations demand substantial computational resources and extended simulation times to capture biomolecular interactions realistically. Fine-tuning parameters, performing energy minimizations, and analyzing trajectories further add to the complexity. Thus, validating these findings through molecular modeling remains a meticulous and resource-intensive step in drug discovery. Given the high computational cost of these simulations and our current resource limitations, we propose that future studies should incorporate such simulations to refine and enhance the accuracy of our findings.

In conclusion, this study provides a predictive and systems-level analysis of the potential molecular targets and pathways of metal–dithiocarbamate complexes in breast cancer. The identified hub proteins, particularly CDK1, CCNA2, CCNB1, and CCNB2, and their associated cell cycle–related pathways highlight promising directions for further investigation. However, these findings remain preliminary and computational in nature. Experimental validation is necessary to confirm the therapeutic relevance of these complexes and to support their potential development as breast cancer drug candidates.

Author Contribution Statement

All authors contributed equally in this study.

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Conflicts of Interest

The authors state that none of the conflicts of interest or known financial or personal ties they are aware of have any bearing on the research provided in this study.

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