Journal of Experimental and Clinical Pharmacy (JECP)
Doi: 10.52365/jecp.v4i2.1119
http://jurnal.poltekkesgorontalo.ac.id/index.php/JECP/
2024, 4(2), 115-128

Research Article

In Silico Exploration of Suruhan Leaves (*Peperomia pellucida*) for Triple-Negative Breast Cancer Therapy Targeting AURKA

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ARTICLE INFO

Received : 01.Jul.2024
Revised : 20.Aug.2024
Accepted : 27.Aug.2024

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ABSTRACT

Breast cancer is the most common type of cancer worldwide. One of the most widely used chemotherapeutic agents in the treatment of breast cancer is doxorubicin. However, doxorubicin has been reported to cause side effects. Suruhan (*Peperomia pellucida*) contains bioactive compounds that might protect against breast cancer cells. This study aims to analyze the bioactive compound activity of Suruhan leaves in triple-negative breast cancer in silico. The study was conducted by reviewing published literature on bioactive compounds in Suruhan leaves, predicting the protein target, analyzing the gene expression in triple-negative breast cancer (TNBC) patients, analyzing the protein interactions, and examining patient survival. There are five common bioactive compounds in Suruhan leaves, including peperomin A; 6,8-dihydroxy kaempferol 3,6,7,4'-tetramethyl ether 8-neohesperidoside; dillapiole; carotol; and pellucidin A. AURKA is a target protein for bioactive compounds that are also overexpressed in TNBC patients. AURKA has strong interactions with many proteins, including TPX2, NEDD9, CCNB2, CDC20, PLK1, BIRC5, INCENP, TACC3, TP53, and MYCN. The AURKA has emerged as a promising target for TNBC therapy.

Keywords: Drug discovery; ethnopharmacology; *Peperomia pellucida*; triple-negative breast cancer

eISSN 2775-1368

INTRODUCTION

Breast cancer is the most common type of cancer. Around 2.3 million women are diagnosed with breast cancer, with 685,000 deaths globally in 2020 (World Health Organization 2023). In Indonesia, the incidence of breast cancer is 42.1 in the 100,000 population, with an average mortality rate of 17 (Kementerian Kesehatan RI 2023). Yogyakarta has a relatively high incidence of breast cancer among other provinces in Indonesia, which continued to increase from 2008 to 2019 (Ng et al. 2023). Breast cancer occurs due to the interaction of genetic and environmental factors. Starting with the abnormal growth of breast cells, cancer can spread to other areas and trigger other symptoms (Nounou et al. 2015). Genetic mutations in cancer cells support this condition. The most dominant gene mutations in breast cancer cases are PALB-2, BRCA1, and BRCA2 gene mutations (World Health Organization 2023). External factors can increase the risk of breast cancer, including sex, age, obesity, alcohol consumption, family history, radiation exposure, and tobacco use (Purwanti, Syukur, and Haloho 2021; World Health Organization 2023).

Breast cancer is a heterogeneous disease with phenotypic and molecular variation (Lüönd et al. 2021). This variation is the basis for classifying breast tumors into three main subtypes, i.e., luminal A/B with estrogen and/or progesterone receptors, HER2 positive, and triple negative. Compared to other breast cancers, TNBC is recognized as having a more aggressive clinical course. Conventional therapies are often ineffective, leading to cancer recurrence. TNBC is particularly challenging to treat due to the lack of specific receptors on the cancer cells (Mahmoud, Ordóñez-Morán, and Allegrucci 2022).

Various efforts have been made to prevent and suppress the incidence of breast cancer. Popular breast cancer treatments can be performed with chemotherapy, breast removal surgery, immunotherapy, and gene therapy (Nounou et al. 2015) . The development of effective therapies in the treatment of breast cancer is needed to reduce the number of deaths. One of the most widely used chemotherapeutic agents in the treatment of breast cancer is doxorubicin. However, it is toxic to normal cells, including cardiotoxicity, hepatotoxicity, and nephrotoxicity. Also, Sun et al. (2022), observed that doxorubicin can increase DCAF13 expression in breast cancer cells. This suggests that doxorubicin chemotherapy may increase the risk of metastasis in breast cancer cells. The long-term use of doxorubicin can also cause resistance (Du et al. 2021). The development of chemoresistance often undermines therapeutic efficacy, necessitating innovative approaches against TNBC.

Co-chemotherapy emerges as a promising strategy to address the complexities of TNBC. Combining multiple chemotherapy agents with distinct mechanisms of action aims to enhance cancer cell killing, overcome resistance, and ultimately improve overall survival rates. Co-chemotherapy combines

chemotherapeutic and chemopreventive agents, such as natural or synthetic substances. *Peperomia pellucida*, a ubiquitous herb with traditional medicinal applications (Rovik et al. 2024), has garnered scientific attention for its potential anticancer properties. While research is still in its early stages, promising findings suggest its efficacy against breast cancer. Suruhan (*Peperomia pellucida*) contains anticancer bioactive compounds, especially in the leaves. It has cytotoxic activity against many cancer cell lines, including breast cancer cell MCF-7 (Al-Madhagi et al. 2018; Clemen-Pascual, Macahig, and Rojas 2021; Angelina et al. 2024). This study aims to analyze the bioactive compound activity of Suruhan leaves (*Peperomia pellucida*) in triple-negative breast cancer in silico.

MATERIALS AND METHODS

Method

Literature Review of Bioactive Compounds in Suruhan Leaves

The search for studies that tested the bioactive content in Suruhan leaves was performed on the Scopus database of publications in the last ten years. Five expected and dominant bioactive compounds were used for further analysis. The structure of bioactive compounds was retrieved from PubChem at https://pubchem.ncbi.nlm.nih.gov/

Protein Target Prediction

The target of five dominant bioactive compounds of *P. pellucida* in human proteins is searched at http://www.swisstargetprediction.ch/. The compound's chemical structure was taken from the PubChem page, and the canonical SMILES were copied to the Swiss Target Prediction page. This is useful for predicting off-targets of the molecules.

Analysis of Gene Expression in Triple-Negative Breast Cancer Patients

Gene expression analysis in TNBC patients is available through the UALCAN website at https://ualcan.path.uab.edu/analysis.html. Furthermore, an overlapping analysis of protein targets and genes was performed. Data from protein target analysis were combined with gene expression analysis of TNBC patients to see common target proteins and genes through the Interactivenn website at https://www.interactivenn.net/

Analysis of Protein Interaction

Protein interaction analysis was performed using the STRING website at https://string-db.org/ with a cell division of 4.00 (moderate). We considered the eleven highest-ranked genes for further assessment.

RESULTS

Suruhan has diverse metabolite compounds ranging from leaves to stems to components in each part of the plant body, and most of the bioactive components in Suruhan are found in the leaves. Most of the metabolite compounds found were dominated by peperomin A, 6,8-dihydroxy kaempferol 3,6,7,4'-tetramethyl ether 8-neohesperidoside, dillapiole, carotol, and pellucidin A compounds (Table 1; Figure 1).

Table 1. The Chemical Structure of Five Common and Dominant Bioactive Compounds of Suruhan Leaves

Bioactive Compounds	References	PubChem ID	Structure
Peperomin A	(Gomes et al. 2022)	11486787	$C_{22}H_{22}O_8$
6,8-dihydroxy kaempferol 3,6,7,4'-tetramethyl ether 8-neohesperidoside	(Su Xu et al. 2005; Kurniawan et al. 2016)	44260050	$C_{31}H_{38}O_{17}$
Dillapiole	(François et al. 2013; Ruslan et al. 2021; Verma et al. 2015)	10231	$C_{12}H_{14}O_4$
Carotol	(Ruslan et al. 2021; Verma et al. 2015; De Oliveira et al. 2017)	442347	$C_{15}H_{26}O$
Pellucidin A	(Gomes et al. 2022)	637244	$C_{22}H_{28}O_6$

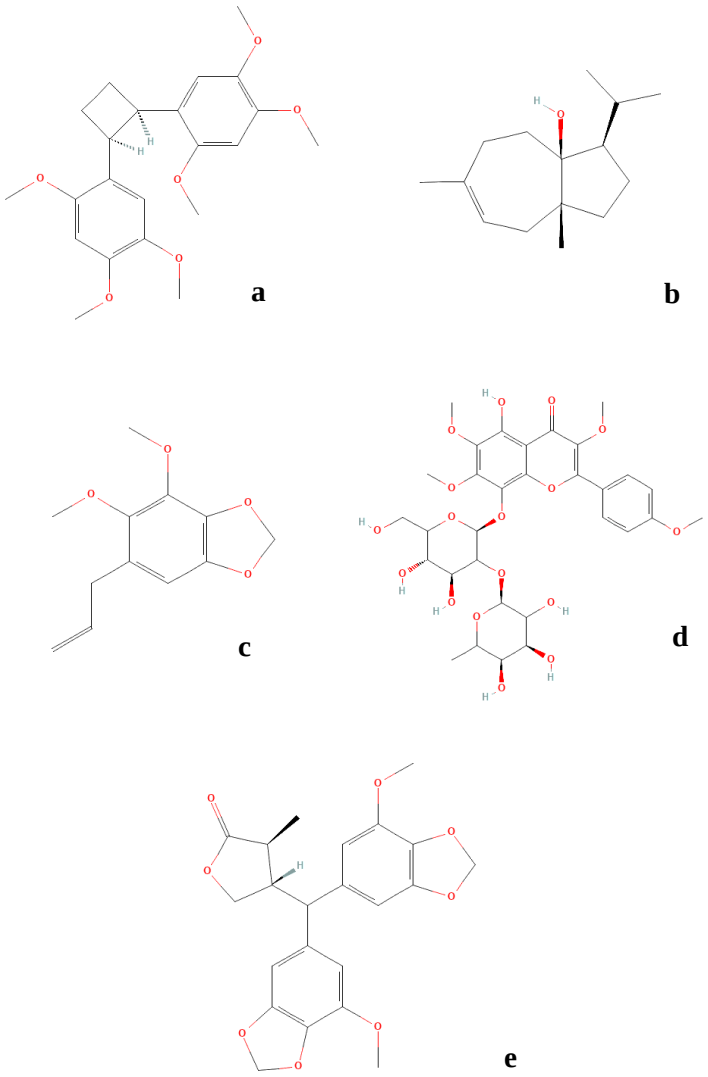

Figure 1. The structure of the bioactive compounds of Suruhan leaves: peperomin A (a), 6,8-dihydroxy kaempferol 3,6,7,4'-tetramethyl ether 8-neohesperidoside (b), dillapiole (c), carotol (d), and pellucidin A (e)

Table 2. Target Proteins of Bioactive Compounds of Suruhan Leaves in Human Cells

Bioactive Compounds	Total of Target Proteins in Human Cells
peperomin A	111
6,8-Dihydroxykaempferol 3,6,7,4'-tetramethyl ether 8-neohesperidoside	102
dillapiole	103
carotol	106
pellucidin A	111
doxorubicin drug	102

The target activity of bioactive compounds against human proteins was searched at http://www.swisstargetprediction.ch/. There were more than 100 gene/protein targets by Suruhan's bioactive compounds (Table 2).

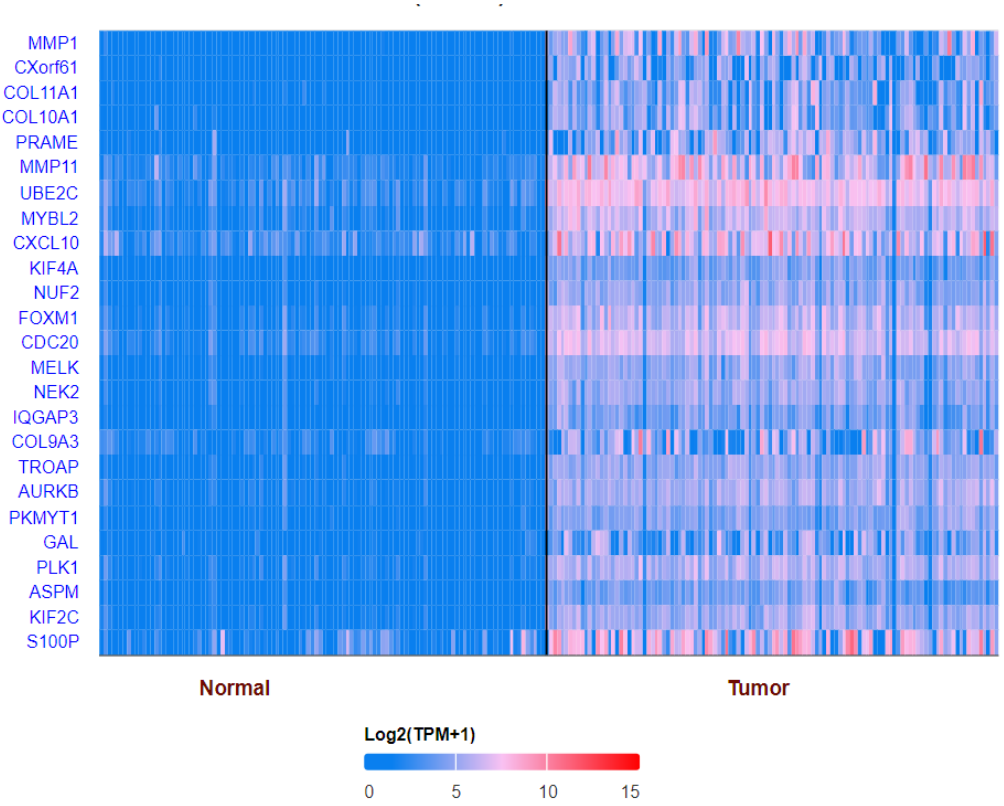

Figure 2. Protein expression analysis (up-regulated proteins) in TNBC patients

In the heatmap, the colors indicate the expression levels of different genes. The color scale at the bottom indicates the expression level, with blue representing low expression and red representing high expression. This heatmap provides a visual overview of how gene expression differs between normal and TNBC patients. Genes with significantly different expression levels between the two groups are potential biomarkers or therapeutic targets. A total of 250 up-regulated genes were downloaded for further analysis, including MMP1, CCNA2, AURKA, AURKB, PLK1, TYMS, TYMP, CHEK1, CDC7, CDC25B, KIF11, and others (Figure 2). Suruhan's bioactive compounds have targeted many common proteins and genes. For example, peperomin A targets AURKB, AURKA, CCNA2, and PLK1 proteins (Table 3).

Table 3. Common Proteins and Genes Target Bioactive Compounds of Suruhan leaves

Bioactive Compounds	Common Proteins and Genes Targeted in TNBC Patients
peperomin A	AURKB AURKA CCNA2 PLK1
6,8-dihydroxy kaempferol 3,6,7,4'-tetramethyl ether 8-neohesperidoside	MMP1 CCNA2 AURKA TYMS TYMP CHEK1 SQLE
dillapiole	CCNA2 CHEK1 AURKA CDC7 CCNE1 PBK TYMP
carotol	SQLE CDC25B KIF11 AURKA
pellucidin A	AURKB AURKA CCNA2 PLK1
doxorubicin drug	MMP1 TOP2A CDK1 AURKA TYMP

The analysis showed that the most common target is the AURKA protein. Aurora kinase A (AURKA) is a mitotic serine/threonine kinase that regulates cell cycle progression. During mitosis, it associates with the centrosome and spindle microtubules. It is essential in various mitotic events, such as mitotic spindle formation, centrosome duplication, separation, maturation, chromosomal alignment, spindle assembly checkpoint, and cytokinesis (STRING Consortium, 2023; https://string-db.org/).

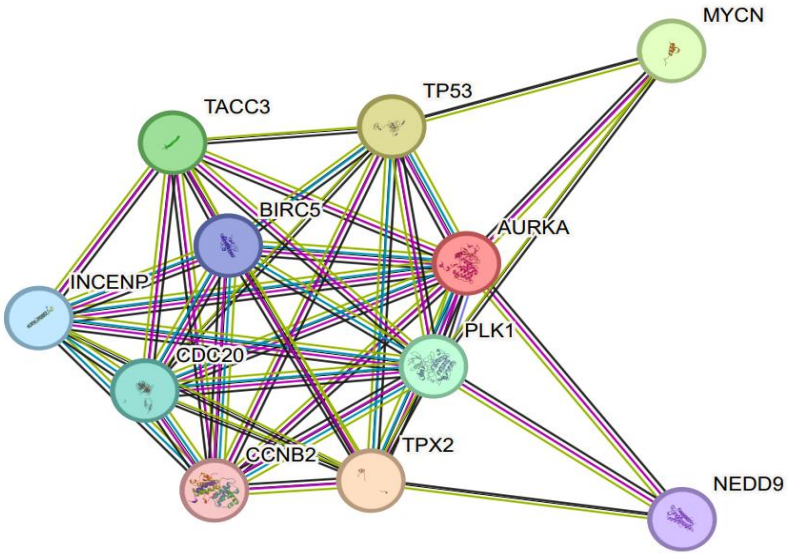

Figure 3. Analysis of interactions between target protein (AURKA) in TNBC cells

AURKA protein interacts strongly with several functional proteins, including TPX2, NEDD9, CCNB2, CDC20, PLK1, BIRC5, INCENP, TACC3, TP53, and MYCN (Figure 3). These proteins are important in cell division and proliferation (Table 5).

Table 5. Protein-to-protein Interaction (STRING Consortium, 2023 at https://string-db.org/)

Protein	Function
TPX2 (Targeting protein for Xklp2)	It is a spindle assembly factor required for the regular assembly of mitotic spindles. Required for regular assembly of microtubules during apoptosis. Required for chromatin and kinetochore-dependent microtubule nucleation. Mediates AURKA localization to spindle microtubules.
TP53 (Cellular tumour antigen p53)	It acts as a cancer suppressor in many cancer types and induces growth arrest or apoptosis depending on the physiological circumstances and cell type. It is involved in cell cycle regulation as a trans-activator that negatively regulates cell division by controlling a set of genes required for this process. One of the activated genes is an inhibitor of cyclin-dependent kinases.
MYCN (N-myc proto-oncogene protein)	It positively regulates the transcription of MYCNOS in neuroblastoma cells.
TACC3 (Transforming acidic coiled-coil-containing protein 3)	It plays a role in the microtubule-dependent coupling of the nucleus and the centrosome. It is involved in the processes that regulate centrosome-mediated interkinetic nuclear migration of neural progenitors. Acts as a component of the TACC3/ch- TOG/clathrin complex proposed to stabilize kinetochore fibers of the mitotic spindle by acting as the inter-microtubule bridge.
PLK1 (Serine/threonine-protein kinase PLK1)	It is a serine/threonine protein kinase that performs several essential functions. fMAD2L1 regulates its phase of the cell cycle, including regulating centrosome maturation and spindle assembly, removing cohesins from chromosome arms, inactivating anaphase-promoting complex/cyclosome (APC/C), and inhibiting mitotic exit and cytokinesis.
Component CDC20 (Cell division cycle protein 20 homologs)	It is required for the total ubiquitin ligase activity of the anaphase-promoting complex/cyclosome (APC/C) and may confer substrate specificity upon the complex. MAD2L1 regulates it: In metaphase, the MAD2L1-CDC20-APC/C ternary complex is inactive, and in anaphase, the CDC20-APC/C binary complex is active in degrading substrates.
INCENP (Inner centromere protein)	It is a chromosomal passenger complex (CPC) component that acts as a critical regulator of mitosis. The CPC complex has essential functions at the centromere in ensuring correct chromosome alignment and segregation. It is required for chromatin-induced microtubule stabilization and spindle assembly. It acts as a scaffold regulating CPC localization and activity.
BIRC5 (Baculoviral IAP repeat-containing protein 5)	It is a multitasking protein with dual roles in promoting cell proliferation and preventing apoptosis. It is a component of a chromosome passage protein complex (CPC), which is essential for chromosome alignment and segregation during mitosis. cIt may also transmit a critical regulator of the localization of this complex; it directs CPC movement to different locations from the inner centromere during prometaphase to the midbody during cytokinesis and participates in the organization of the center spindle by associating with polymerized microtubules.
NEDD9 (Enhancer of filamentation p55)	It is a docking protein that plays a central coordinating role for tyrosine-kinase-based signaling related to cell adhesion. It may also transmit growth control signals between focal adhesions at the cell periphery and the mitotic spindle in response to adhesion or growth factor signals initiating cell proliferation.
CCNB2 (G2/mitotic-specific cyclin-B2)	It is essential to control the cell cycle at the G2/M (mitosis) transition.

DISCUSSION

Suruhan (*Peperomia pellucida*) has diverse metabolite compounds from each part, and most of the bioactive components are found in the leaves. There are some dominant compounds in Suruhan leaf, including peperomin A, 6,8-dihydroxy kaempferol 3,6,7,4'-tetramethyl ether 8-neohesperidoside, dillapiole, carotol, and pellucidin A. Research has shown that extracts from *Peperomia pellucida* exhibit cytotoxicity against various cancer cell lines, including breast cancer. The bioactive compounds in Suruhan can inhibit the growth of MCF-7 breast cancer cells in vitro (Al-Madhagi et al. 2018; Angelina et al. 2024; Clemen-Pascual, Macahig, and Rojas 2021). The bioactive compounds inhibit cancer cell growth by inducing apoptosis, stopping the cell cycle, inhibiting carcinogens, and inhibiting kinases (Majrashi et al. 2023). Interestingly, these extracts seem non-toxic to normal cells (Moorthi, Vasantha, and Maruthasalam 2018). This selectivity is crucial for potential cancer therapies.

Triple-negative breast cancer (TNBC) is an aggressive form of breast cancer that is characterized by the lack of expression of estrogen, progesterone, and HER2 receptors. This makes TNBC cancers challenging to treat with traditional hormone therapies and targeted therapies (Mahmoud, Ordóñez-Morán, and Allegrucci 2022). As a result, there is a significant unmet need for new therapeutic strategies for TNBC patients. It drove co-chemotherapy development to increase the potency of chemotherapeutic agents and reduce therapeutic side effects.

More than 250 up-regulated genes in TNBC patients represent potential targets for new therapies (Figure 2). By understanding the function of these genes and their encoded proteins, we might identify vulnerabilities in TNBC cells. Targeting these vulnerabilities could lead to developing drugs that inhibit TNBC growth or survival. All bioactive components in the Suruhan leaves identified the AURKA protein as the most targeted protein (Figure 3). Aurora kinase A (AURKA) is a protein that regulates the cell cycle. AURKA is overexpressed in various cancers, including TNBC (Du et al. 2021). This study investigated the interaction between compounds and AURKA in TNBC cells. Its overexpression in breast cancers leads to aggressive cancer proliferation with increased neoplastic stem cell phenotype and ability to migrate and invade (Du et al. 2021; Winter et al. 2023). Therefore, it has emerged as a promising target for TNBC therapy.

AURKA is overexpressed in TNBC compared to healthy breast tissue. This overexpression suggests a role in TNBC development and progression. The mechanisms underlying the regulation of AURKA in cancer cells include gene amplification, gene mutation, microRNA regulation, and transcriptional to post-

transcriptional modifications (Du et al., 2021). AURKA also interact strongly with various other proteins including TPX2, NEDD9, CCNB2, CDC20, PLK1, BIRC5, INCENP, TACC3, TP53, and MYCN (Figure 3). The interaction between AURKA and various types of proteins causes the development and proliferation of cancer cells. Survival analysis showed that patients with higher expression levels of AURKA have a higher risk of recurrence (Siggelkow et al. 2012). This suggests that AURKA expression can lead to poor prognosis through faster cancer cell growth, higher metastatic potential, and more excellent resistance to therapy; therefore, inhibiting AURKA expression can reduce cancer cell aggressiveness.

One promising approach for developing new cancer therapies is using small molecules that target critical proteins involved in cancer cell growth and survival, including AURKA. However, not all up-regulated genes necessarily promote cancer. Some might be part of the body's natural defense mechanisms against cancer. We must differentiate between genes contributing to TNBC and those with a protective role. Identifying the up-regulated genes is just the first step. Understanding what proteins these genes encode and their specific functions within the TNBC cells is crucial to knowing which proteins offer the most promising targets for therapeutic intervention. More studies are needed to isolate and identify the specific bioactive compounds in *Peperomia pellucida* that might target AURKA. Understanding the mechanism of action would be crucial to assessing these compounds' effectiveness and potential side effects.

Combining a potent chemotherapy drug with a plant-based compound could enhance the treatment effect. However, this needs to be rigorously tested in clinical trials. While there is substantial research on doxorubicin's efficacy against TNBC, combining AURKA inhibitors with doxorubicin might be more effective. This approach could target different aspects of the cancer and potentially overcome resistance mechanisms.

CONCLUSIONS

There are five dominant bioactive compounds in Suruhan leaves, including peperomin A; 6,8-dihydroxy kaempferol 3,6,7,4'-tetramethyl ether 8-neohesperidoside; dillapiole; carotol; and pellucidin A. AURKA is a target protein for bioactive compounds that are also overexpressed in TNBC patients. AURKA has strong interactions with many proteins, including TPX2, NEDD9, CCNB2, CDC20, PLK1, BIRC5, INCENP, TACC3, TP53, and MYCN. The overexpression of AURKA and its involvement in crucial cellular processes make it a promising target for developing new treatments for TNBC.

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