Jurnal Ners Volume 9 Nomor 2 Tahun 2025 Halaman 2975 - 2980
JURNAL NERS
Research & Learning in Nursing Science
http://journal.universitaspahlawan.ac.id/index.php/ners

THE ROLE OF MEDICAL CHEMISTRY IN THE SYNTHESIS OF SELECTIVE ANTICANCER COMPOUNDS FOR BREAST CANCER WITH A COMPUTATIONAL AND EXPERIMENTAL APPROACH

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Abstract

Breast cancer is a cancer with high prevalence in women and requires more selective therapy and minimal side effects. Medicinal chemistry plays an important role in the development of anticancer compounds through a chemical synthesis approach, in silico modeling, and in vitro validation. The aim of this study is to comprehensively review the role of medicinal chemistry in the synthesis and development of selective anticancer compounds in breast cancer, with an emphasis on computational (in silico) approaches and experimental validation as two inseparable aspects of the modern drug discovery and development process. This study examined twenty articles related to natural and synthetic compounds tested for cancer targets such as HER-2, CDK4, and DAPK1. Compounds such as luteolin and benzimidazole derivatives show high affinity and cytotoxic activity in MCF-7 cells. The results show that the integration of computational and experimental approaches supports the development of breast cancer therapy that is more effective and safe.

Keywords*: breast cancer, medical chemicals, in silico, molecular docking, anticancer compounds.*

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INTRODUCTION

Breast cancer is one of the most common cancer that attacks women around the world. According to Global Burden of Cancer (Globocan) data in 2020, there were more than 2.26 million new cases of breast cancer with a mortality rate of 684,996 people, making it the second highest cause of death after lung cancer in women (Sibuh et al., 2021). In Indonesia alone, breast cancer contributes around 16.6% of the total cases of cancer with a number of deaths of more than 22,000 cases, showing the urgency of more optimal treatment.

Risk factors for breast cancer are complex and multifactorial. (Rianti et al., 2012) identify that the risk of breast cancer is closely related to age, a history of benign tumors, family history, first menstrual age, first gestational age, and hormonal and genetic influences. The use of hormonal contraception and modern lifestyle also exacerbates the prevalence of breast cancer in various developing countries.

At present, conventional therapy such as chemotherapy, radiotherapy, and surgery are still the main line in the treatment of breast cancer. However, this approach is often accompanied by serious side effects such as hair loss, digestive system disorders, extreme fatigue, and decreased quality of life of patients (Shofi, 2021) In addition, cancer cell resistance to chemotherapy drugs further strengthens the urgency to develop alternative therapy that is more selective, effective, and minimal toxicity.

In this context, medical chemistry plays a strategic role as an interdisciplinary discipline that integrates organic chemistry, biochemistry, pharmacology, and computational technology for designing and synthesizing bioactive compounds with specific activity on the molecular target of the disease, includingCancer (Nurfadhila et al., n.d.). Structure-based approaches such as Quantitative Structure-Activity Relationship (QSAR), Molecular Docking, and ADMET Predictions have revolutionized the process of drug discovery with high efficiency in time and cost(Dwi Ananto et al., 2020; Ino Ischak et al., 2023) .

The In Silico approach allows researchers to evaluate the bioactivity potential of compounds against cancer target protein such as HER-2, CDK4, and DAPK1 without the need to directly conduct biological tests (Dwi Ananto et al., 2020). In addition, synthesis and biological tests in vitro and in vivo remain an important step to validate the results of the computing simulation and assess the pharmacodynamic and toxicology effects as a whole (Amin, Meithasari, et al., 2025)

Various natural compounds such as luteolin, Palmarumycin CP1, dihydrochempferide, and bernerin derived from herbal plants have shown promising anticancer activities in in silico and texperimental studies. These compounds not only show high affinity against breast cancer target protein, but also have an ADMET profile that supports further as a drug candidate (Noer & Khairullah, n.d.) (Fadlan et al., 2022)

However, some compounds still show potential side effects such as mutagenicity or carcinogenity, which demands further toxicological analysis. Therefore, the synergy between computational and experimental approaches is an ideal strategy in the development of selective and safe anticancer compounds.

Based on this background, this article aims to review comprehensively the role of medical chemistry in the synthesis and development of selective anticancer compounds on breast cancer, with an emphasis on the computational approach (in silico) and experimental validation as twoThe integral side of the process of discovery and development of modern drugs.

METHODS

This study was conducted with a literature study approach (literature review) of twenty scientific articles that discussed specifically design, synthesis, activity evaluation, and validation of anticancer compounds for breast cancer through medical chemical approaches. The main focus of this study is to critically examine the synthesis method of compounds, molecular computing approaches (in silico), prediction of pharmacokinetics and toxicity of compounds through predictive devices, and biological experimental tests on breast cancer cells, especially MCF-7 cell lines. These articles were obtained from national and international accredited scientific journals such as Jambura Journal of Chemistry, Pharmaceutical magazine, Udayana Pharmacy Journal, and Indonesian Journal of Science. Article selection criteria are based on the year of publication in the last five years, focusing on research related to breast cancer, and includes the use of relevant computational experimental techniques and/or approaches, such as Molecular Docking, QSAR (Quantitative Structure-Activity Relationship),and cytotoxic test in vitro.

The computational approach (in silico) is applied as an initial stage in filtering and evaluating the potential of compounds against breast cancer target protein, such as HER-2 (GDP ID: 3PP0), CDK4 (GDP ID: 2W96), and DAPK1 (GDP ID: 5AUX, 5AV3). The three -dimensional structure of the target protein is obtained from the Bank Data Protein Database (GDP), while the compound structure is prepared in the .PDB or .MOL2 format using software such as Chem3D, Marvinsketch, or Avogadro, then converted into the format of .PDBQT with Autodock Tools. Docking simulation is carried out by autodock vina or MOE (Molecular Operating Environment) to

evaluate ligand affinity on the active site of protein.

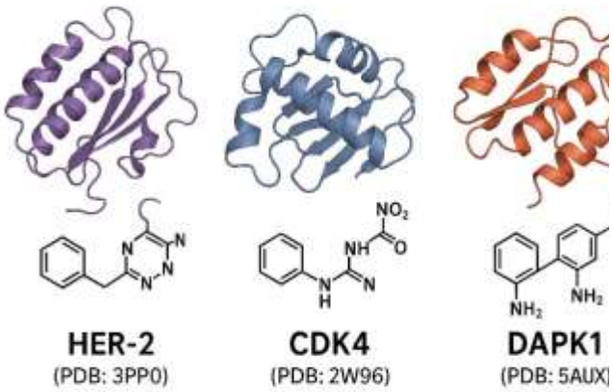

Figure 1. Illustration of Protein Her-2, CDK4, and Dapk1 and its liga for the docking simulation in breast cancer. (image generated by AI using DALL·E, OpenAI, 2025)

The main parameters observed include bond -free energy values (ΔG), hydrogen and hydrophobic bonding interactions, ligand binding positions to active residues, as well as RMSD values from the redocking process as a form of validation of the method. As an illustration, Ischak et al. (2023) reported that the Palmarumycin CP1 compound shows an excellent affinity of HER -2 with a ΔG value of -9.2 kcal/mol, as well as a strong interaction with the TYR735 residue. Meanwhile, dihydrochempferide interacts with dapk1 protein with a value of ΔG -6.9 kcal/mol, forming important interactions through flavonoid hydroxyl groups with LYS42 residues.

In addition to docking, the prediction of pharmacokinetics and toxicity is carried out using two main platforms, namely Swissadme and PreADMET. Swissadme is used to evaluate parameters that reflect the pharmaceutical feasibility of a compound, such as compliance with lipinski's rule of five, logp, molecular weight, number of donors and hydrogen bonding acceptors, and topological polar surface areas (TPSA). On the other hand, preADMET is used to predict the nature of ADMET test compounds, including absorption (HIA and CaCO-2 model), distribution (penetration of brain/BBB blood barrier and plasma/PPB protein bonds), metabolism (predictions of interaction with the enzyme CYP450), and toxicity (mutagenicity and carcinogenicity based on the ames test and animal model). For example, a study by (Prasiska Wulandari et al., 2023)) of luteolin compounds show that although this compound meets the RO5 parameter, toxicity predictions indicate the existence of mutagenic potential, so further experimental validation is needed.

Some articles analyzed also involved chemical synthesis methods and experimental biological tests. (Dwi Ananto et al., 2020)) designing and synthesizing the Meisoindigo derivative using the AM1 semi empiris approach and validating it through QSAR analysis to determine the relationship between chemical structures and biological activity of the CDK target.

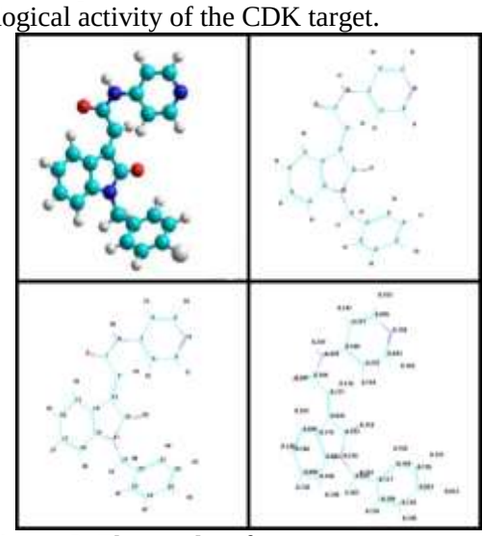

Figure 2. The results of geometry optimization from Meisoindigo parent compound using the Balls and Cylinders model Available on the Hyperchem program package. Atom C is depicted with a blue ball young, atom O with red, an atom with dark blue and H atoms with white. Then the compound depicted with the sticks model. (from Dwi Ananto et al., 2020)

Validation of biological activity is carried out through in vitro tests using the MTT Assay or SRB Assay method in MCF-7 breast cancer cells. The main parameter measured in this test is the IC50 value, which is the concentration of compounds that can inhibit the growth of 50% of the cancer cell population.

Seny Uji	Log 1/IC50 eksperimen	Log 1/IC50 prediksi			
		model 1	model 4	model 6	model 9
1	4.85	-6.24	5.20	5.09	5.41
5	5.49	-5.95	5.57	5.60	5.27
11	5.21	-7.16	5.35	5.13	5.44
19	4.35	-4.73	4.08	4.41	4.52

Figure 3. Comparison Data of Log 1/IC50 Experiment Value with Log 1/IC50 Prediction (from Dwi Ananto et al., 2020)

In the study of (Amin, Meithasari, et al., 2025), Compound 1- (4-Tert-buttilbenzoiloxi) Urea is proven to have IC50 of 59.15 µg/ml against MCF-7 cells, much better than hydroxyurea which only has IC50 of 430.21 µg/ml. This shows that the modification of chemical structures through the medical chemical approach has succeeded in significantly increasing the anticancer potential.

Data analysis in this study was carried out qualitatively and quantitatively by comparing various key parameters of each approach used. The value of ΔG of docking results is compared between test compounds and standard ligands to

assess the strength of bond affinity. ADME prediction value compared to lipinski feasibility standards and FDA recommendations to evaluate the suitability of compounds as potential drugs. The IC50 value of biological tests compared to standard drugs such as tamoxifen or doxorubicin. QSAR validation in terms of statistical correlation strength, including the coefficient of determination (R), root mean square error (RMSE), and the level of significance (P-value). All of this data is then integrated to identify compounds that show optimal balance between the strength of affinity to the target, good pharmacokinetic profile, and high biological effectiveness as candidates for selective anticancer compounds to breast cancer.

RESULTS AND DISCUSSION

The role of medical chemistry in the development of selective anticancer compounds is very visible through various synthesis studies of new compounds based on computational and experimental approaches. One example is shown (Sibuh et al., 2021)) which succeeded in synthesizing two thiosemicarbazone derivatives, namely 3-methoxybenzaldehyde Thiosemicarbazone (3-MBTSC) and 4-Nitrobenzaldehyde Thiosemicarbazone (4-NBTSC). Both of these compounds show very strong cytotoxic activity against MCF-7 breast cancer cells, with IC50 values of 2.82 µg/ml and 2.80 µg/ml respectively.

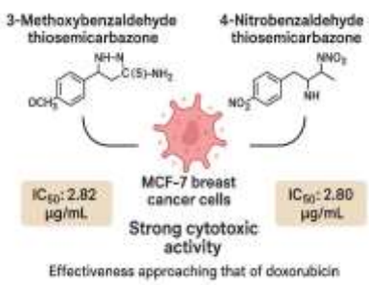

Figure 4. the strong cytotoxic activity of 3-methoxybenzaldehyde and 4-nitrobenzaldehyde thiosemicarbazones against MCF-7 breast cancer cells with IC_{50} values near that of doxorubicin. (image generated by AI using DALL·E, OpenAI, 2025)

Not only that, the expression of oncogene genes such as race and CCPs proved to have decreased, while the expression of tumor pressure genes such as Pten and BRCA1 increased significantly. This finding indicates that the two compounds have a mechanism of work multitarget and is very potential to be further developed as a selective anticancer drug candidate.

Another study by (Abbade et al., 2024) developed the compound alkylsulfonyl benzimidazole, where two derivatives namely compounds 23 and 27 show high affinity of BCL-2 protein-the main regulator of the apoptosis pathway-with docking scores of −9,6 and −9.2 kcal/mol. The gene expression test in MCF-7 cells induced by this compound also shows a significant decrease in BCL-2 expression, which supports the pro-apoptotic activity of these compounds.

Figure 5. Docking results from AutoDock Vina: (a) Compound 23 in Bcl-2 site; (b) Compound 27 pose; (c) Binding energy comparison with vincristine as reference. (from Abbade et al., 2024)

Examining dihydrochempferide compounds which show potential as Dapk1 protein inhibitors, one of the important targets in the breast cancer apoptosis pathway (Fadlan et al., 2022). Docking results show bond energy values of -6.9 and -5.7 kcal/mol against two isoform protein Dapk1 (5AUX and 5AV3), while ADMET predictions show that this compound has good absorption and distribution properties and minimal toxicity. With the basic structure of flavonoids, this compound confirms the importance of flavonoid frames in selective anticancer design.

On the other hand, the medical chemical approach is also used to design Meisoindigo derivatives as CDK4 inhibitors, important protein in cell cycle regulations(Dwi Ananto et al., 2020) applies an AM1 and QSAR semimpiris approach and finds a significant correlation between biological structure and activity, with the coefficient of determination r of 0.926. This finding shows that the modification of aromatic and cyclic nitrogen groups is very influential in increasing the affinity of compounds to the target.

In addition to the synthesis of compounds, the exploration of natural materials is also an integral part of the development of selective anticancer (Noer & Khairullah, n.d.) show that luteolin, a flavonoid compound from Parsley (petroselinum crispum), has high affinity against HER -2 and JAK2 protein, with bond energy between -8.0 to -10.5 kcal/mol. Although the results of the ADME prediction indicate the potential for mutagenic and carcinogenic, this compound remains promising as an initial candidate that needs further validation. Research by (Ino Ischak et al., 2023) also shows that Palmarumycin CP1, a metabolic compound from Gorontalo herbal plants, is able to interact actively with TYR735 residues on HER -2 with bond energy -9.2 kcal/mol. Together with Curcumin and Tembaritine compounds, these compounds meet the criteria for Lipinski's Rule of Five, which indicates the feasibility of the therapeutic compounds.

Meanwhile, (Yunita Sari & Febrina, 2023) in a study of more than 30 herbal plants, reported that several compounds such as eugenol (cloves), vitexin (centers), mangiferin (kasturi), and peonidin (purple sweet potato) showed affinity that was competitive of bonds, withThe value of ΔG

ranges from -6.3 to -10.8 kcal/mol. This shows that herbal compounds have great potential as alternative or complementary therapies with lower toxicity.

The progress of medical chemistry is also reflected in the strategy of synthesis and structural modification that is right on target. (Amin, Meithasari, et al., 2025) succeeded in synthesizing compounds 1- (4-tert-buttilbenzoiloxi) Urea which shows cytotoxic activity is higher than hydroxyurea, with an IC50 value of 59.15 µg/ml compared to 430.21 µg/ml in MCF-7 cells. This effectiveness shows that the structural -activity approach (SAR) is very important in directing more selective molecular synthesis.

The computational approach plays a central role in accelerating and filtering candidates for anticancer compounds. (Nurfadhila et al., n.d.) emphasizes that the integration of molecular docking, QSAR, ADMET predictions, and pharmacophore modeling is an important component in the early stages of drug design. Study by (Cui et al., 2020) also supports that the In Silico approach is able to cut time and costs in the initial screening process. In the study of (Abbade et al., 2024), the Molecular Dynamics simulation during 200 NS shows that compounds 23 and 27 have high stability on the active BCL-2 protein site, which strengthens the validity of docking predictions.

Furthermore, (Amin, Pratama, et al., 2025) and (Yuliani, et al., 2025) highlighted the importance of the integration of computational and experimental approaches as the optimal strategy in the development of anticancer compounds. Software such as Autodock, Swissadme, PreADMET, and Marvinsketch are the main devices in this study. With the increasingly widespread application of artificial intelligence (AI) and machine learning, the prediction process, screening, and optimization of compounds can be done faster and more accurately. However, computational results must still be biologically validated through in vitro and in vivo tests so that they can be developed into effective and safe clinical drugs.

CONCLUSION

Medical chemistry plays an important role in the development of selective anticancer compounds to breast cancer, through the integration of computational and experimental approaches. Various synthetic and natural compounds have shown significant biological activity on molecular targets such as HER-2, CDK4, and DAPK1, both through in Silico simulations and in vitro tests.
In Silico approaches such as molecular docking and ADMET predictions allow the screening of compounds quickly and efficiently, while experimental validation ensures its effectiveness and safety. Compounds such as luteolin and benzimidazole derivatives show the potential as a drug candidate, although it still requires optimization and further testing.

Thus, the combination of chemical synthesis strategies, computational modeling, and biological validation is the key in designing breast cancer therapy that is more selective, effective, and safe.

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