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Review: Development of Natural Materials as Breast Cancer Anticancer

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ABSTRACT

Objective: *This study aims to review various efforts in developing anticancer therapies based on medicinal plants and synthetic compounds, particularly for breast cancer, which has high prevalence and mortality rates.* ***Method:*** *Data were collected through a literature review of scientific journals published between 2010 and 2020. The study analyzed the potential of various medicinal plants and bioactive compounds using both experimental and computational approaches.* ***Results:*** *The review revealed that medicinal plants such as soursop leaves, galangal, moringa leaves, Kasumba Turate flowers, and red dragon fruit peels exhibit significant anticancer potential. Their activities include cytotoxicity, proliferation inhibition, and apoptosis induction in T47D and MCF-7 breast cancer cells. Additionally, an in silico approach was employed to evaluate bioactive compounds like galangin and quercetin, which demonstrated potential interactions with specific molecular targets such as HER-2 and SIRT1.* ***Novelty:*** *This study highlights the importance of exploring both natural and synthetic anticancer compounds to develop more effective and safer therapies. The integration of in silico analysis provides a deeper understanding of molecular interactions, supporting the advancement of targeted breast cancer treatments.*

INTRODUCTION

Cancer is one of the most dangerous degenerative diseases. Additionally, it is the second leading cause of death worldwide, with as many as 9.6 million deaths recorded in 2018, World Health Organization, 2018. Cancer is characterised by the continuous and uncontrolled abnormal growth of cells, which then invades the body's biological tissues [1]. Cancer is a complex disease characterised by prolonged proliferation signal transduction, decreased growth suppression, reduced cell death, continuous replication, stimulation of angiogenesis, and invasion and metastasis. This capability of cancer occurs due to genetic instability [2].

Cancer is a disease with the highest prevalence that can lead to death, one of which is breast cancer. The mortality rate due to breast cancer continues to rise, leading to the development of various treatment methods to prevent fatalities [3]. In breast cancer, uncontrolled cell proliferation originates in the terminal duct lobular unit (the functional part of the breast), caused by several factors, including family history, gene mutations involved in DNA repair, hormonal factors, poor lifestyle, and environmental factors [4].

The development of breast cancer therapy is still crucial to increasing the recovery rate, reducing recurrence, lowering mortality, and improving patients' quality of life. Most women with breast cancer undergo several surgical procedures. Surgery is often combined with other treatments such as radiation therapy, chemotherapy, hormone therapy, and targeted therapy. However, chemotherapy drugs have strong side effects, not only killing cancer cells but also attacking healthy cells. Therefore, the discovery of new compounds with anticancer properties is continuously pursued, ranging from

medicinal plants to newly synthesised drugs through drug development and new drug discovery via structural modifications.

RESEARCH METHOD

The data used in writing this journal review were collected using a literature study method, including primary and secondary sources. Literature searches were conducted using online-based literature search tools such as NCBI PubMed and Google Scholar. The keywords used for the literature search included "anticancer," "breast cancer anticancer," "anticancer activity," and "breast cancer." The collected literature was then structured accordingly, and data on breast cancer anticancer activity were compiled in tabular form. The journal review was written following the prescribed format. The literature study results included ten journals from 2014–2020 containing information on breast cancer anticancer activity, which will be presented in tables, along with several sources providing information on the condition of breast cancer in Indonesia.

RESULTS AND DISCUSSION

In the study conducted by Pertiwi, W., et al., the effect of soursop leaf extract on the viability of T47D breast cancer cell lines was observed, indicated by a decrease in cell viability percentage as the extract concentration increased across three incubation periods [1]. The extract concentration that inhibited 50% of cell viability was found to be 569.8 µg/ml at 24 hours, 431.6 µg/ml at 48 hours, and 94.26 µg/ml at 72 hours of incubation. The study results showed that soursop leaf extract only began to inhibit the growth of T47D breast cancer cell lines after 72 hours.

The flavonoids contained in soursop leaves have anticancer effects by inhibiting cell growth and kinase activity, inducing apoptosis, suppressing the expression of matrix metalloproteinases and invasive tumour behaviour, and acting as an antiproliferative agent. In addition to flavonoids, acetogenins found in soursop leaves exhibit cytotoxic effects on cancer cells by inhibiting mitochondrial complex I, leading to reduced ATP production, inducing apoptosis, activating p53, and halting the cell cycle at the G1 phase, resulting in cell death.

The study conducted by Nuraini, M. focused on the compound galangin extracted from galangal (Alpinia galanga) and its potential as a breast cancer anticancer agent. This study employed a computational (in silico) approach to analyse the interaction of galangin with the HER-2 receptor, a crucial target in breast cancer therapy [5]. The methods used included molecular docking and molecular dynamics to predict the activity of galangin as a protein inhibitor. The analysis results indicated that galangin met Lipinski's Rule of Five criteria, suggesting good pharmacokinetic properties, such as low molecular weight, appropriate lipophilicity, and an optimal number of hydrogen bonds. Furthermore, galangin exhibited a favourable binding energy with the HER-2 receptor, though not as strong as the original ligand. This study concluded that galangin has potential as a safe and effective breast cancer drug candidate and can be further developed for clinical trials.

The study conducted by Muna, L. N., & Maulidinah, F. demonstrated that the cytotoxic activity of a single aqueous extract of moringa leaves was tested using the MTT assay method [6]. The principle of this method involves a colorimetric measurement of the formation of water-insoluble purple formazan salts, which result from the reduction reaction of water-soluble tetrazolium, producing a yellow-coloured solution [7]. The cytotoxic test of the aqueous moringa leaf extract used various concentration levels, namely 31.25; 62.5; 125; 250; 500; and 1000 µg/ml. In this study, testing the aqueous extract of moringa leaves with increasing test compound concentrations did not affect cell viability percentage, resulting in an IC50 value of more than 1000 µg/ml. A compound with an IC50 value exceeding 1000 µg/ml is considered less potent for development as a cytotoxic agent, Machana et al., 2011. The observations of the cytotoxic test of the aqueous moringa leaf extract can be seen in Table 1 and the linear regression equation curve in Figure 1.

Table 1. Stotoxicity test results of Moringa leaf water extract.

Kon-sentrasi µg/ml	viabilitas sel (%)				
	v1	v2	v3	rata-rata	SD
1000	109,11	105,63	108,65	107,80	1,89
500	101,32	105,70	107,49	104,84	3,17
250	99,99	106,91	106,96	104,62	4,01
125	100,74	106,40	104,68	103,94	2,90
62,5	95,69	98,20	97,19	97,03	1,27
31,25	103,06	94,91	96,27	98,08	4,37

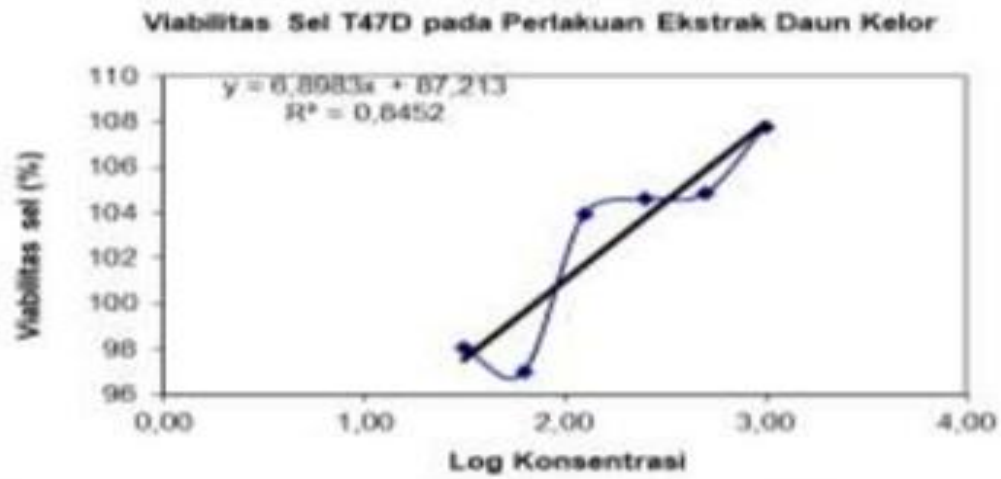

Figure 1. Linear regression equation of cell viability (x) and log concentration (x).

The compounds contained in moringa leaves that play a role as anticancer agents are antioxidants, which can inhibit oxidative stress and thus prevent the formation of cancer cells. Additionally, potassium is also present, which can degrade cancer cells, Bhattacharya et al., 2018.

Based on microscopic observations in the cytotoxicity test of moringa leaves, morphological changes in T47D cells and changes in cell density were observed. Consequently, the higher the concentration of aqueous moringa leaf extract used, the

more it alters cell morphology (cells appear rounded), cells appear to be floating, cell density changes, and cells do not adhere to each other. The morphology of T47D cells after treatment with aqueous moringa leaf extract can be seen in Figure 2.

Figure 2. Morphology of T47D breast cancer cells after 24 hours incubation. Control T47D cells (A), Moringa leaf water extract concentration 250µg/ml (B), Moringa leaf water extract concentration 500 250µg/ml.

The single cytotoxic activity of doxorubicin was used at several concentration levels, namely 0.625; 1.25; 2.5; 5; 10 and 20 µg/ml. Doxorubicin in this study was used as a positive control, so the higher the concentration used, the more significant the effect on the decrease in % cell viability. In this test, the IC50 of doxorubicin in the T47D cytotoxicity test was found to be 8.17 µg/ml. A test compound has good cytotoxic effects if the IC50 is less than 100 µg/ml, Machana et al., 2011. The results of the doxorubicin cytotoxicity test observations can be seen in Table 2, as well as the linear regression equation curve in Figure 3.

Table 2. Results of dxorubicin stitotoxicity test.

Kon-sentrasi µg/ml	viabilitas sel (%)				
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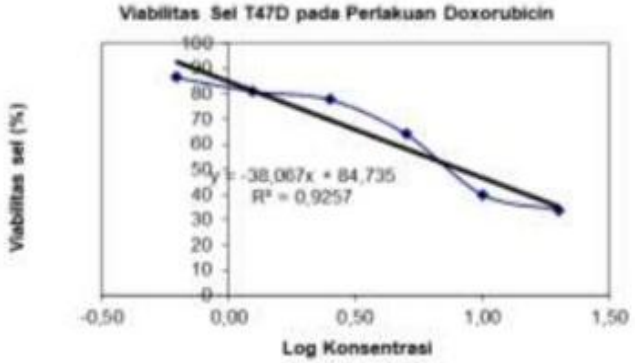

Figure 3. Linear regression equation of cell viability (Y) and log concentration (X).

The mechanism of action of doxorubicin involves intercalation with DNA and inhibition of DNA and RNA synthesis by disrupting the template and causing steric hindrance. Additionally, doxorubicin interacts with topoisomerase II by forming a DNA cutter, Fita et al., 2015. The morphology of T47D cells after doxorubicin treatment can be seen in Figure 4.

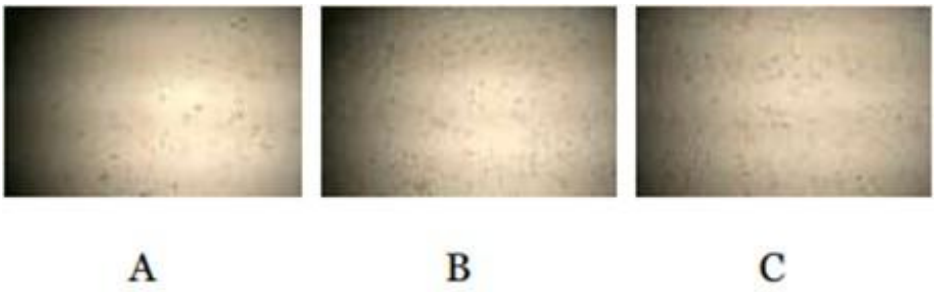

Figure 4. Morphology of T47D breast cancer cells after 24 hours incubation. Doxorubin concentration 20µg/ml (A), Doxorubicin concentration 5µg/ml (B), Doxorubicin concentration 1.25µg/ml (C).

Fitria et al. (2011) research showed that the ethanolic extract of ciplukan herb (EC) has cytotoxic effects against MCF-7 breast cancer cells, with an IC50 value of 118 µg/mL. The active components of EC, such as saponins, flavonoids, polyphenols, and physalin, provide pharmacological activity, including the ability to reduce cancer cell viability. EC also affects cell morphology, where dead cells appear round and float.

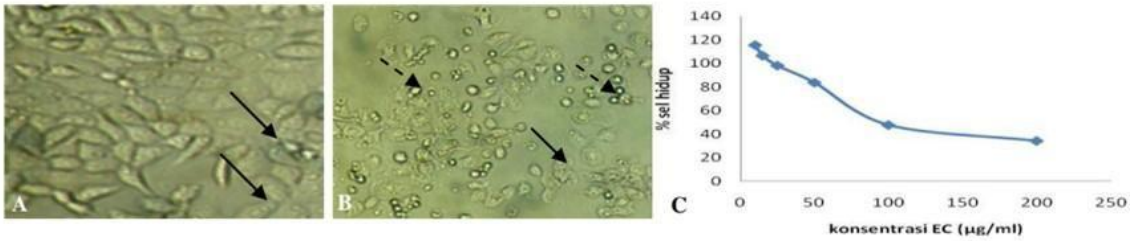

Figure 5. EC concentration.

EC has been proven to induce apoptosis in MCF-7 cells through a mechanism involving inhibition of the anti-apoptotic protein Bcl-2 in the NFκB/PI3K/Akt pathway, cytochrome c release, and activation of the caspase pathway. Due to CASP-3 gene deletion in MCF-7 cells, apoptosis is likely mediated through caspase 6, 7, and 9. Additionally, EC increases p53 expression, which induces pro-apoptotic proteins such as Bad and Bax. With its cytotoxic properties and ability to induce apoptosis, EC has the potential to be developed as a chemopreventive agent for breast cancer treatment.

Amir and Murcitro research demonstrated that Phaleria macrocarpa ("Mahkota Dewa") has potential as an herbal anticancer drug, particularly for breast cancer. This plant contains flavonoids, polyphenols, saponins, tannins, and steroids, which exhibit antioxidant and anticancer activity. Testing using the MTT assay method yielded an IC50 value that supports its use as an alternative treatment.

Table 3. Correlation between concentration and absorbance for each MCF7 cell line in the cytotoxicity test of methanol extract of p. Macrocarpa leaves.

Konsentrasi (µg/mL)	Absorbansi	Rata rata	Korelasi
60	0,230, 0,230, 0,222, 0,213, 0,222, 0,250, 0,233, 0,213, 0,260, 0,230, 0,230, 0,236	0,236	
30	0,210, 0,192, 0,240, 0,335, 0,170, 0,180, 0,170, 0,163, 0,230, 0,201, 0,155, 0,160	0,199	
15	0,160, 0,110, 0,211, 0,153, 0,144, 0,245, 0,280, 0,140, 0,382, 0,266, 0,150, 0,140	0,198	
7,5	0,190, 0,220, 0,220 :0,180, 0,190, 0,327, 0,290, 0,220, 0,242, 0,380, 0,180, 0,310	0,245	R = -0.372
3,75	0,200, 0,283, 0,190, 0,204, 0,200, 0,263, 0,241, 0,188, 0,221, 0,286, 0,204 0,230	0,224	R^2= 0.138
1,875	0,230, 0,300, 0,290, 0,280, 0,230, 0,281, 0,310, 0,275, 0,341, 0,334, 0,204, 0,200	0,278	
0,9375	0,213, 0,250, 0,262, 0,290, 0,213, 0,310, 0,220, 0,220, 0,310, 0,240, 0,224, 0,220	0,247	
0	0,190, 0,194, 0,215, 0,305, 0,305, 0,250, 0,282, 0,280, 0,261, 0,265, 0,310, 0,236	0,257	

Table 3 presents the absorbance measurement results of MCF7 cells using methanol extract of P. macrocarpa leaves at various concentrations. The IC50 value of the methanol extract is 15 µg/mL, where MCF7 cell viability decreases with increasing or decreasing concentration. The correlation between extract concentration and MCF7 cell absorbance is weak (R = 0.372, R^2 = 0.138).

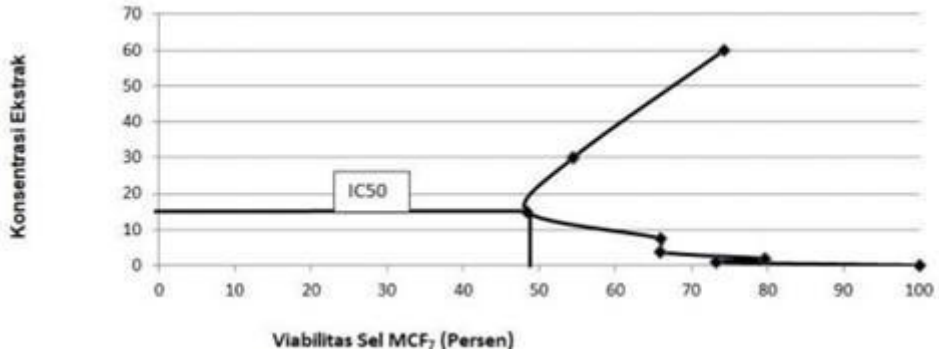

Figure 6. Cytotoxicity graph of methanol extract of p. Macrocarpa leaves against MCF-7 cancer cells.

This extract significantly reduces cell viability at concentrations <30 µg/mL, although antagonistic interactions among chemical components may diminish its anticarcinogenic and antitumor effects. Further research at concentrations around IC50 is needed to explore its impact on cell morphology and biological activity. Chemical compound characterization is also essential to understand the level of cytotoxicity and the effectiveness of breast cancer treatment.

Cahyani et al. research developed microsphere capsules of licorice (Glycyrrhiza glabra) extract as an extended-release oral preparation for breast cancer therapy [8]. The focus was on inhibiting HMGB1 protein, which plays a role in cancer metastasis, and determining the optimal concentration of sodium tripolyphosphate (TPP) as a cross-linking agent.

In silico testing showed that active compounds such as glycyrrhetic acid, liquiritin apioside, and liquiritin have potential as HMGB1 inhibitors with high binding affinity and low toxicity. The microsphere capsule formulation was made using the ionic gelation method with TPP variations (3%, 6%, and 9%). The formula with 3% TPP provided the

best results in quality evaluation, including particle size, moisture content, disintegration time, and weight uniformity.

This study concluded that licorice extract has potential as an adjunct breast cancer therapy with a microsphere system that provides prolonged therapeutic effects.

Research conducted by Malik, F et al. investigated the cytotoxic activity of safflower (Carthamus tinctorius Linn) flower extract against T47D breast cancer cells [9]. This plant is known to contain various secondary metabolites with potential as anticancer agents.

Table 4. Results of phytochemical screening of ethanol extract of kusumba turate flowers (*Carthamus tinctorius Linn*).

Uji Kandungan Senyawa	Reagen	Hasil	Kesimpulan
Alkaloid	*Dragendorff*	Terbentuk endapan jingga	+
Flavanoid	Mg + Hcl	Merah jingga	+
Saponin	Air + HCl 2 N	Tidak terbentuk busa/buih stabil	-
Tanin	FeCl3		+
Steroid dan Terpenoid	*Lieberman-Buchard*	Hijau	-
		merah kekuningan	+

Note: (-) : does not contain secondary metabolite compound groups; (+) : contains secondary metabolite compound groups.

The results showed that safflower flower extract contains compounds such as alkaloids, flavonoids, tannins, and terpenoids.

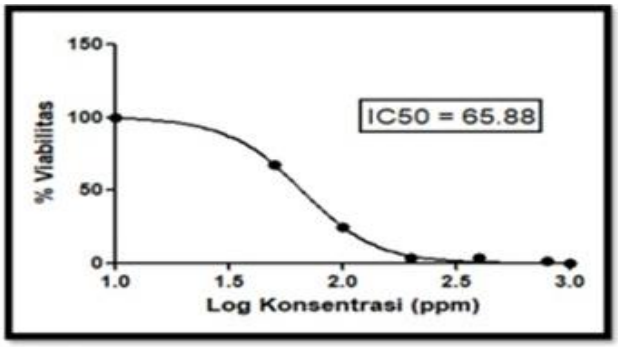

Figure 7. Log curve of concentration vs % cell viability against 5-Fu.

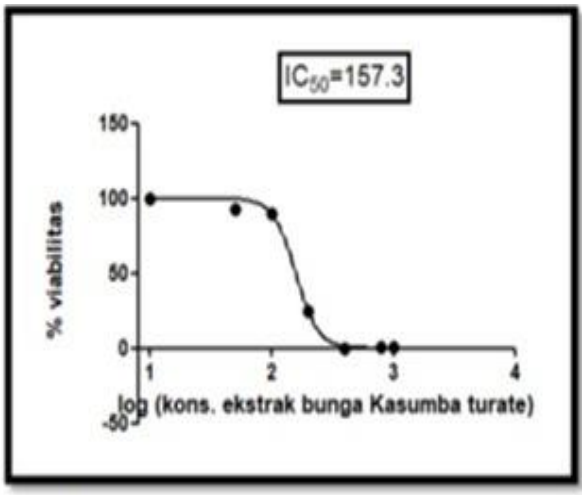

Figure 8. Log curve of concentration vs % cell viability of extract.

Cytotoxicity testing indicated that the IC50 value of safflower flower extract was 157.3 ppm. This result suggests that safflower flower extract has a fairly good activity against cancer cells. During testing, T47D cell viability gradually decreased as the extract concentration increased. Based on the data presented in Figure 2, at a concentration of 157.3 ppm, it was able to inhibit T47D cell proliferation by up to 50%. Although the IC50 value of this extract is higher than the positive control 5-Fluorouracil, this result still provides a positive indication of the extract's potential as an anticancer agent. Thus, safflower flower extract has the opportunity to be further developed in future cancer therapy research.

Research conducted by Sarasmita MA & Laksimiani explored the cytotoxic potential of ethanolic extract from red dragon fruit peel (Hylocereus polyrhizus) against MCF-7 breast cancer cells [10]. The cytotoxicity test results showed that the extract exhibited significant cytotoxic activity with an IC50 value of 387.49 µg/mL.

This cytotoxic mechanism is primarily due to the inhibition of IκB kinase (IKK), leading to NF-κB inactivation and inhibiting cancer cell proliferation. Additionally, red dragon fruit peel is rich in flavonoids, which provide antioxidant properties, potentially reducing reactive oxygen species (ROS) and preventing cancer development. This study highlights the importance of in vitro testing as a more cost-effective and ethical alternative to in vivo testing.

These findings indicate that red dragon fruit peel can be developed as a natural anticancer agent, offering new hope for breast cancer treatment.

Research conducted by Muh. Shofi focused on the interaction analysis of quercetin, a compound found in the leaves of the Kencana Ungu plant, with the Sirtuin1 enzyme, which acts as a breast cancer agent [11]. In this study, the quercetin binding affinity was found to be -7.3 kcal/mol, indicating a strong interaction with the enzyme. However, the docking of quercetin with the Sirtuin1 enzyme was suboptimal, as indicated by an RMSD value exceeding 2 Å. This suggests that although the interaction is strong, the resulting conformation may not be completely stable.

Further analysis revealed that quercetin forms hydrogen bonds with 16 amino acid residues in the Sirtuin1 enzyme, including Glu420, Leu418, and Lys377. The types of interactions involved include van der Waals bonds, Conventional Hydrogen Bonds, and Pi-Anion interactions, demonstrating the complexity of interactions between quercetin and the target enzyme.

These interactions have the potential to inhibit enzymatic activity involved in cell cycle regulation, which may contribute to breast cancer therapy development.

Table 5. Binding affinity and RMSD values.

Binding Affinity (Kkal/mol)	RMSD/Ub	RMSD/Lb	Rerata RMSD
-7.3	6.935	4.869	5.902

Figure 9. Tethering of sirtuin 1 enzyme with quercetin.

Research conducted by Raihan, M., & Tukiran focused on the anticancer potential of carbazole alkaloids isolated from Murraya microphylla as inhibitors of SIRT1 and CDK9 [12]. This study successfully identified isomahanimbine and mahanimbine as SIRT1 inhibitors, as well as girinimbine and koenigine as CDK9 inhibitors.

All these compounds exhibited lower binding energy compared to control inhibitors, indicating their potential as anticancer agents. The binding energy for SIRT1 ranged from -9.5 to -11.2 kcal/mol, while for CDK9, it ranged from -7.7 to -10.7 kcal/mol. Lower binding energy values indicate higher affinity, meaning these compounds can inhibit SIRT1 and CDK9 more effectively than existing control inhibitors.

CONCLUSION

Fundamental Finding : Various medicinal plants and newly synthesized compounds have demonstrated potential anticancer activity against breast cancer. Plants such as galangal, ciplukan, purple ruellia, chalcone, licorice root, mahkota dewa, moringa, murraya, and sesewanua leaves, along with the synthetic compound 1-(4-Trifluoromethylbenzoyloxymethyl)-5-Fluorouracil, exhibit diverse mechanisms including anticancer, chemopreventive, cytotoxic, apoptotic, and proliferation inhibition effects on breast cancer cell lines T47D, MDA-MB-231, and MCF-7, as well as inhibition of SIRT1 and CDK9. **Implication :** The findings suggest that natural and synthetic compounds could serve as promising candidates for breast cancer treatment. Their diverse bioactivities indicate potential applications in targeted therapy, drug development, and complementary treatments, highlighting the need for further pharmacological evaluation and clinical translation. **Limitation :** Despite promising in vitro results, limitations remain in terms of bioavailability, toxicity, and clinical efficacy. The lack of comprehensive in vivo and clinical studies restricts the direct application of these compounds in medical practice, necessitating further validation. **Future Research :** Future studies should focus on in vivo evaluations, mechanistic investigations, and clinical trials to assess the safety, efficacy, and pharmacokinetics of these compounds.

Additionally, exploring novel formulations and combination therapies may enhance their therapeutic potential against breast cancer.

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