RESEARCH ARTICLE

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Exploring the *In Vitro* Anticancer Potential of Indonesian Medicinal Plants and Natural Compounds for Breast Cancer Therapy

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Abstract

Objective: This review aims to explore the potential of Indonesian medicinal plants as therapeutic agents for breast cancer in in vitro studies. **Methods:** The review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and the Population, Intervention, Comparison, Outcome, and Study design (PICOS) framework. Electronic databases, including Pubmed, ScienceDirect, Scopus, SpringerLink, Medline, and Google Scholar, were searched for articles published in English from October 2019 to 2024. Based on the PICOS framework, eligibility criteria are focused on original preclinical studies that addressed the biological activity of extracts or isolates from Indonesian medicinal plants using breast cancer cell lines. **Result:** In all, 74 plants from 38 families that are grown in Indonesia were presented as potential therapeutic and chemopreventive agents that may reduce cancer growth, spread, or recurrence. Steroid glycosides, curcumin, pinostrobin, alphitolic acid, isoxanthochymol, 4β,10α-dihydroxyaromadendrane, 4α,10α-dihydroxyaromadendrane were revealed as cytotoxic agents with inhibitory effects on breast cancer cell proliferation and migration. These compaunds were also found to prevent metastasis by suppressing cancer cell adhesion and to induce apoptosis in in vitro studies. Seven Indonesian medicinal plants Begonia sp., Garcinia celebica, Cryptocarya pulchrinervia, Aglaia harmsiana, Syzygium aqueum, Kaempferia pandurata Roxb., and Curcuma xanthorrhiza Roxb. were shown to significantly inhibit breast cancer cell proliferation, with IC50 values of less than 20 µg/mL. **Conclusion:** This review article could be a key to further develop the potential of natural products from Indonesian medicinal plants for cancer treatment and prevention, including their roles as chemosensitizers, immunotherapeutics, in combination therapies with other anticancer drugs, in novel formulations, and in elucidating the molecular mechanisms underlying their anticancer properties. Furthermore, toxicology evaluation also needs to be studied in detail through the clinical trial stage.

Keywords: Breast cancer- Indonesia medicinal plant- In vitro study- Natural compounds- Anticancer agent

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Introduction

In 2021, BC will be the most prevalent kind globally, making about 11.7% of all cases, according to the Global Cancer Observatory. Cancer cases will continue to increase in 2040 to 30.2 million. Breast cancer incidence and mortality rates vary significantly across Asia, close to half of the breast cancer patients (45.4%) were diagnosed in Asia [1–3]. Breast cancer was also the most common cause of cancer mortality among women in five ASEAN countries (ASMR: Philippines 21.5, Malaysia 19.3, Singapore 17.8, Vietnam 14.7, Indonesia 14.4) [1]. In 2020, Indonesia reported 396,914 new cancer cases. The most common types were breast cancer (16.6%), cervical cancer (9.2%), lung cancer (8.8%), colorectal cancer (8.6%), and liver cancer (5.4%). This represents a 13.8% increase compared to 2018 [4].

Based on data from the Badan Riset Inovasi Nasional (BRIN), there are 2,850 species of medicinal plants growing in Indonesia. Furthermore, more than 22,000 traditional medicinal plants have been scientifically identified. The nation has traditionally used the plants to treat a variety of illnesses, including cancer. There are many natural substances found in Indonesian medicinal plants that have therapeutic qualities, such as terpenoids, alkaloids, flavonoids, triterpenoids, phenolic, and essential oils [5-6]. These substances are being researched for their potential in contemporary medications in addition

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to their application in traditional medicine. Several medicinal plants that have been used for centuries by local communities in Indonesia, including Curcuma genus, Brucea javanica, Boesenbergia pandurata, Caesalpinia sappan, and Nigella sativa. Interestingly, these medicinal plants target several hallmarks of cancer, and even Curcuma genus exhibited biological activities that target all hallmarks of cancer [7-8].

Integration of Traditional and Complementary Medicine (TCM) into health care systems in cancer has been recommended by WHO, but it is particularly important to emphasize that these treatments are evidence-based and safe to use, and not as a substitute for conventional cancer treatment [9]. In addition, TCM in cancer treatment is useful as a preventive and maintenance therapy. This area is of significant interest due to the widespread for usage of herbal plants by the Indonesian society to cure various diseases [10–14].

In vitro studies are essential tools in cancer research, offering a controlled environment for testing new therapies [15-16]. These studies help identify promising compounds, predict clinical responses, and advance pharmacogenomic research [17-18]. This systematic review aims to explore the therapeutic potential of Indonesian medicinal plants as in vitro agents for breast cancer treatment.

Materials and Methods

Protocol and Registration

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards served as the parameters for the protocol and systematic review (SR) [19]. We did not register the protocol.

Eligibility Criteria

The review focused on original in vitro studies that used breast cancer cell lines to investigate the biological activity of extracts or isolates from Indonesian medicinal plants. The inclusion criteria in this systematic review were based on the preclinical PICOS (population, intervention, comparison, outcome, study design) approach:

Population: human breast cancer cell lines.

Intervention: the extraction, fractionation, or isolation of Indonesian medicinal plants for therapeutic purposes.

A comparator is a control group or comparison that is not given any treatment, has chemotherapy or radiation therapy for known cancer, or gets treatment with other drugs.

Anticancer action (cell viability, death, cell cycle arrest, and/or cell proliferation in vitro) and protein expression levels are controlled as a result.

Research design: research with no baseline or a comparable one.

Human clinical trials, epidemiological studies, theses, dissertations, case studies, editorials, letters to the editor, duplicate studies discovered in multiple databases, non-laboratory studies, articles with the full version unavailable, articles written in a language other than English, and removed articles were among the criteria used to exclude the studies. Additionally disqualified were studies that did not examine the anticancer potential of breast cancer cell lines or that mixed Indonesian plant extract with other medications.

Search Strategy

The search strategy will be developed using a combination of Medical Subject Headings (MeSH) and keywords together with Boolean operators as follows: ('Indonesian medicinal plants' or 'Indonesian medicinal herbs') and ('breast cancer' or 'mammary cancer') and ('cell line' or 'in vitro'). The search was performed in pubmed, ScienceDirect, Scopus, SpringerLink, Medline, and Google Scholar databases. The articles selected are those published between October 2019 and October 2024 (5 years). The references of eligible articles will also be screened for relevant studies. Gray literature or evidence not published in commercial publications will not be included in this review.

Study Selection

All search results and screening processes were exported to the free online systematic review management software Rayyan [20]. Citations obtained from electronic database searches were compiled into a web-based application known as Rayyan, a semi-automatic artificial intelligence tool for identifying studies used in systematic reviews. Additionally, this tool made it easier to find and eliminate duplicate content. In order to find possible papers to be included in the review, two independent reviewers then filtered the citations' titles and abstracts according to the eligibility requirements. In particular, the criterion included pertinent data about Indonesian medicinal plants' potential for breast cancer treatment based on preclinical research. The following step included evaluating a copy of the articles' whole text. The two reviewers discussed and settled the differences they had found. In the event where reviewers 1 and 2 couldn't agree, a third reviewer was chosen to make the decision. The research analyzers then confirmed the final list of included studies. The PRISMA flow diagram was used to provide a summary of the choices made throughout the selection process, including the total number of citations obtained from the database search using our search keywords, the final number of included studies, and the reasons for exclusion.

Data Extraction

Methods for data extraction/retrieval (e.g., extract data from text or tables, extract data from figures). The data of the included papers was extracted into an electronic spreadsheet. We recovered information regarding the in vitro study (lines cell used); study design (number of experimental groups; method of cytotoxicity evaluation); characteristics of the intervention (taxonomic identification of the species; preparation method of the Indonesian medicinal plant extract; chemical composition; dose; dosage frequency) and identification of the study (authors; year of publication).

The taxonomy and nomenclature of the species used in the studies selected for review, were compared with taxonomic information available in existing standards in a botanical database The Flora on Line (http://www.worldfloraonline.org/) and the articles were classified

according to the available information, enabling the analysis of possible taxonomic errors [21-22].

The main outcomes evaluated was inhibitory concentration (IC_{50}). The secondary outcomes evaluated were: cell viability; cell cycle progression; apoptosis rate; protein and gene expression changes. Furthermore, information on the mechanisms of the signaling pathways and molecular targets studied was also be extracted when available.

Risk of Bias and Quality Assessment

The authors methodically appraised all of the selected studies according to the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) method to judge the quality of evidence. Due to the absence of a standardized protocol for assessing in vitro studies, an adapted RoB tool specifically designed for preclinical research was used [23-24]. The items analyzed were: study design, study limitation, inconsistency, imprecision, publication bias, cytotoxic effect size, and overall quality. The overall quality is indicated as: "high", "moderate", "low" or "very low". Two writers rated the included papers as "high," "moderate," "low," or "very low" quality based on their assessment of each research. When they couldn't agree on the quality, a third author took over to make the ultimate judgment [24-25].

Results

Study Characteristics

As depicted in Figure 1, we have identified 3530 articles by electronic search. After removing the duplicates (n=79), 3372 articles were submitted to a screening of their titles and abstracts. One hundred and seventy six (176) articles were read in full and submitted to evaluation according to the inclusion and exclusion criteria, and eighty four (84) were selected for qualitative synthesis. Ninety two (92) articles were excluded due to the following reasons: results were not reported in quantitative form; IC_{50} values were in the low and non-toxic category; interventions were not from Indonesian medicinal plants, interventions were a combination of extracts and drugs; doses and duration of interventions were not reported.

General characteristics of the studies included in this review are summarized in Supplementary Tables 1 and 2. Supplementary Table 1 describes a variety of Indonesian medicinal plants that have the potential for breast cancer therapy with IC_{50} values categorized as having high and moderate cytotoxic activity. According to the US NCI, cytotoxic activity is classified as follows: An IC_{50} <20 µg/ml indicates high cytotoxic activity, an IC_{50} 21-200 µg/ml indicates moderate cytotoxicity, an IC_{50} 201-500 µg/ml indicates low cytotoxicity, and an IC_{50} >500 µg/ml indicates no cytotoxic activity. Out of the 84 studies, 26 studies exhibited high cytotoxic activity (IC_{50} <20

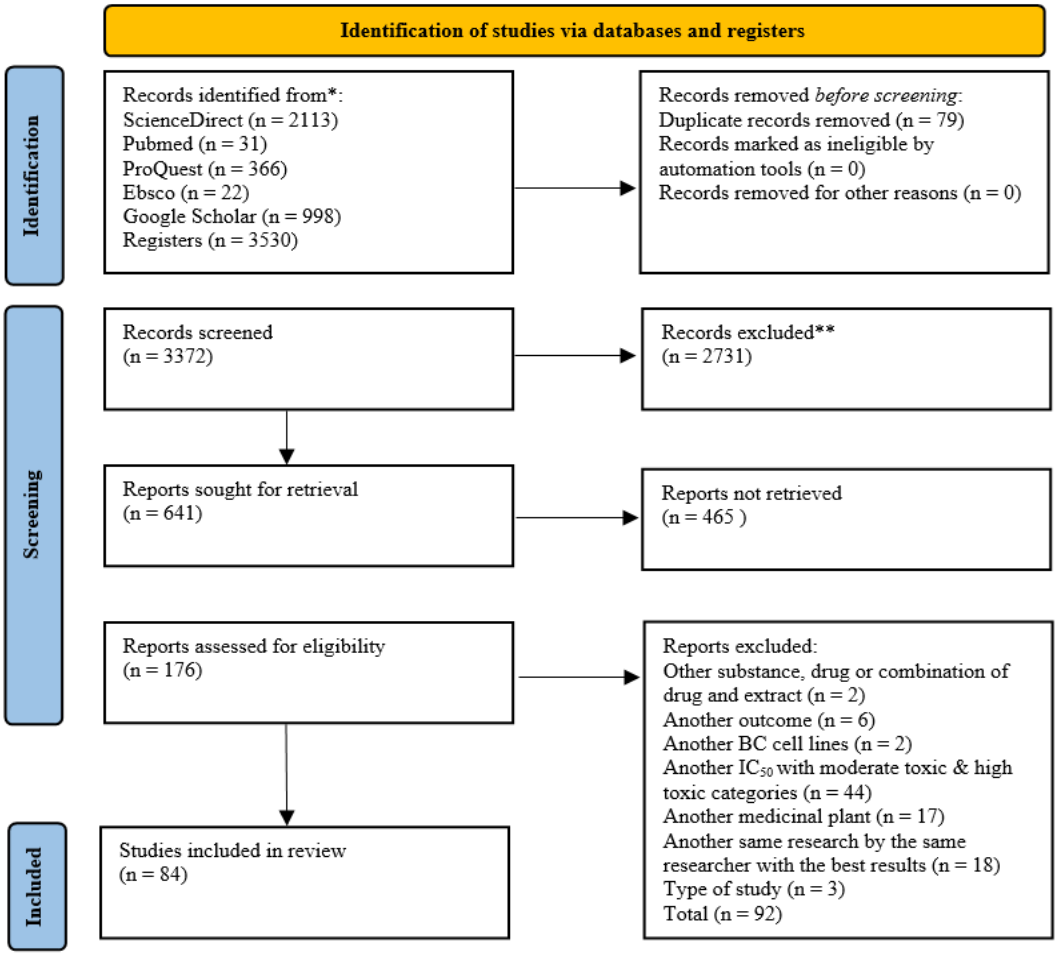

Figure 1. Flowchart of the Selection of Studies on the Indonesian Medicinal Plant Potential for Breast Cancer Therapy

μg/mL), 58 studies showed moderate cytotoxicity (IC_{50} 21-200 μg/mL).

Risk of Bias

We evaluated the research's quality using the GRADE system. Seven studies were classified as high quality, and seventy studies as moderate quality. Research articles that were not included in the two categories were because the recapitulation results showed that the intervention dose and exposure time to breast cancer cell lines were not explained. In addition, of course, the IC_{50} value obtained was not included in the minimum moderate category (NCI). Other studies that were considered not to be included were ongoing studies using the same type of plant, cell lines conducted by the same author/researcher, but only the extract processing process was developed, so we chose the best value from the results of the study.

The article by Sianipar et al. reports three related studies, each focusing on different stages of development (extraction, fractionation, and isolation). Since these studies are based on the same plant species and cell lines, we selected the study with the most effective IC_{50} results, derived from the isolate form of the plant extract [26–28]. Other articles that also do not meet the criteria, even though they have explained the results of research that describes the regulation of the expression of several proteins involved in inhibiting breast cancer cell lines, but do not explain the IC_{50} value, percentage of cell viability, or percentage of cell inhibition, then these articles will not be studied further in this systematic review [29-30].

Synthesis of results

Most Common Cell Lines for Breast Cancer in In Vitro Study

In order to find out how plant extracts affected these breast cancer cell lines, we began looking into research on them. According to our results, numerous cell line types were employed in in vitro study on Indonesian herbal plants, with the following percentages: MCF7 (56%) and T47D (34%), whereas MDA-MB-231 (10%) (Supplementary Table 1). The MCF-7, T47D, and MDA-MB-231 cell lines are commonly utilized in breast cancer research because of their unique traits and usefulness in examining many facets of breast cancer. While MDA-MB-231 is a triple-negative breast cancer cell line used to investigate ER-negative, aggressive breast cancer, MCF-7 is an estrogen receptor (ER)-positive cell line used to represent ER-positive breast cancers. Because T47D expresses a lot of progesterone receptors, it is another ER-positive cell line that is valuable for researching progesterone signaling and the effectiveness of antiprogestins.

Promising Anticancer Indonesian Medicinal Plant Against Breast Cancer Cell Lines

The cytotoxic activity of 74 Indonesia medicinal plants against MCF7, T47D, MDA-MB-231 cells lines were assessed in in vitro study (Supplementary Table 1). Inhibitory concentration (IC_{50}) was used to assess cytotoxicity to obtain prospective anticancer products based on NCI classifies. A crude plant extract is typically deemed to have adequate in vitro cytotoxic activity if the IC_{50} value is less than 20 μg/mL after incubation 48 and 72 hours of treatment of cancer cell lines, according to the US National Cancer Institute (NCI) plant screening program [93].

There have been twenty-one promising Indonesian medicinal plants developed for breast cancer therapy. Thirteen types of Indonesian medicinal plants have been tested on MCF-7 cell lines which have cytotoxic activity with IC_{50} 17 - 1.09 μg/mL, i.e. Annona muricata L. [33], Typhonium flagelliforme [27], Garcinia celebica [42], Hyptis pectinata L. [56], Vitex trifolia L. [57], Cryptocarya pulchrinervia[11], Hibiscus sabdariffa L. [78], Aglaia harmsiana [65], Psidium guajava L. [70], Piper crocatum [75], Morinda citrifolia [78], Boehmeria nivea L. Gaud. [86], Curcuma xanthorrhiza Roxb. [32]. Seven other types of Indonesian medicinal plants have been tested on T47D cell lines and have IC_{50} 16.88 - 0.16 μg/mL, i.e Voacanga foetida (Blume) Rolfe [34], Begonia sp. [37], Vaccinium myrtillus [47], Bauhinia scandens [49], Clitoria ternatea [54], Psidium guava L. [70], Syzygium aqueum [72]. Two types of plants i.e. Curcuma longa [94], Kaempferia pandurata Roxb. [90] have cytotoxic activity IC_{50} 13 and 12.73 μg/mL.

Potential Active Compounds for Breast Cancer Therapy

It is impossible to separate the cytotoxic properties of Indonesian medicinal plants from the existence of active chemicals that may one day be used to treat breast cancer. Acetogenin contained in A. muricata leaf extract may cause a significant reduction in mitochondrial membrane integrity resulting in the induction of apoptosis in breast cancer cells. Determination of compound using thin layer chromatography (TLC) analysis [33]. Steroid glycoside (9(11)α,16(17)β-dioxirane-20,25-dihydroxy-β-sitosterol-3-O-β-glucopyranoside; β-sitosterol-3-O-β-D-glucopyranoside) isolated from Begonia sp. plants have potent inhibitory activity against colon cancer cells. The group of steroid glycoside compounds was analyzed using TLC and nuclear magnetic resonance (NMR) [37]. Isoxanthochymol is a group of polyprenylated benzophenones that have been isolated from the root bark of G. celebica, numerous reports have explained the ability of polyprenylated benzophenones to inhibit various cancer cells growth through multiple mechanisms of action, including apoptosis, cell cycle arrest, and endoplasmic reticulum response. Isoxanthochymol isolated compounds were elucidated by spectroscopic methods including IR, as well as NMR analysis, and were compared with literature data [42]. Saponins and total phenolics were analyzed by spectrophotometer from Bauhinia scandens leaf extract. The phytochemicals in B. scandens leaves could have synergistic interactions, making it a potentially good candidate for anticancer agent screening [49]. Cryptobrachytone C was isolated from the C. pulchrinervia leaves can inhibit proliferation, induce apoptosis, inhibit migration and inhibit colony formation of MCF-7 and T47D cells. The presence of this compound was detected by TLC and NMR11. 4β,10α-dihydroxyaromadendrane and 4α,10α-dihydroxyaromadendrane isolated from A. harmsiana bark extract have high cytotoxic activity in

inhibiting MCF-7 cell proliferation. These compounds were detected by IR spectra and NMR [65]. Alphitolic acid, phytol, phenol, vitamin E, alkaloids, steroids, curcumin, pinostrobin respectively derived from the plants Syzygium aqueum, Piper crocatum, Boehmeria nivea L. Gaud., Kaempferia pandurata Roxb., Curcuma xanthorrhiza Roxb. have almost the same high cytotoxic activity to inhibit the growth of cancer cells [32,72,75,86,90].

The presence of these active compounds may cause high cytotoxic activity against BC cell lines (IC_{50}<20 μg/mL) in the Indonesian medicinal plants studied with an IC_{50} range between 17 - 0.16 μg/mL. This is very promising and will be further developed for breast cancer therapy.

Apoptosis and/or Cell Cycle Arrest

Fourteen research papers published results on apoptosis and/or cell cycle arrest in BC cell lines (Supplementary Table 2). The analytical methods used to investigate cell cycle arrest and apoptosis included acridine orange/ethidium bromide nuclear labeling (2 studies) and flow cytometry (12 publications).

The process of apoptosis/cell cycle arrest would be better if it was carried out at several variations of intervention doses or variations of exposure time, because it would be easier and clearer to provide a description of the stages of the apoptosis/cell cycle arrest process. In addition, it could compare the best dose or exposure time [43,68,85,86]. However, some articles only provided a single dose so that it did not describe the process that occurred [50,76,82,87].

Mechanism Anticancer

The methanolic extract of S. oblongata Mast decreased HER2 mRNA expression to 0.6, 0.25, and 0.33 in comparison to control cells at dosages of $1/2IC_{50}$, $1IC_{50}$, and $2IC_{50}$ μM. On the other hand, doxorubicin reduced HER2 mRNA expression to 0.42 at an IC_{50} of 1 [61].

Compared to untreated cells, administration of an ethanol extract of Curcuma zedoaria (Berg.) Over the course of 24 hours, roscoe at a dosage of 102 μg/mL may increase the expression levels of the proteins caspase-9, caspase-3, and Bax. Western blotting studies showed that ethanol extract decreased the expression levels of Bcl-2 and p38 MAPK in breast cancer cells. The amount of p38 MAPK protein significantly decreased after 48 hours of incubation in the treated medium [87].

Wulandari et al [86] evaluated the expression of the p53, Bcl-2, Bax, Caspase-8, and β-Actin genes triggered by the active fraction of Boehmeria nivea L. Gaud using real-time PCR. In comparison to β-Actin, the CH2Cl2 fraction enhanced the activity of the p53, Bcl-2, Bax, and Caspase-8 genes in MCF-7 cells by 17.03, 6.19, 6.28, and 1.32 times, respectively [86].

To determine how P. macrocarpa leaf extract triggers apoptosis, flow cytometry was used to examine the expression of pro- and anti-apoptotic proteins. One protein that triggers apoptosis is called caspase-3. In comparison to the untreated control group, all group treatments of P. macrocarpa leaves substantially ($p<0.05$) increased caspase-3 activation in a dose-dependent manner (15.9% vs 86.67%, 94.90%, and 96.57%, respectively). Moreover, the caspase-3 level (74.07%) may be raised by the cisplatin group. However, the percentage is lower than that of the treatment with P. macrocarpa leaf extract. Bcl-2 concentration dropped after treatment with P. macrocarpa leaf extract, whereas Bax concentration sharply rose. Bax expression levels showed a dose-dependent rise (24.23%, 42.57%, and 63.47%, respectively) in comparison to the untreated control (19.30%). The Bax/Bcl-2 ratio rises dose-dependently when P. macrocarpa leaves are treated because Bax is elevated and Bcl-2 is downregulated, which promotes the apoptosis that P. macrocarpa leaves cause [85].

Yusuf et al. [36] determined by applying Chromolaena odorata ethanol leaf extract to MCF-7 and T47D breast cancer cells and observing the expression of the Bcl-2 protein using immunocytochemical methods. This suggests that Bcl-2 expression has decreased as a result of the extract's treatment. The expression of the Bcl-2 protein decreased as the ethanol extract from Chromolaena odorata leaves increased in concentration. The anti-apoptotic protein Bcl-2 is expressed more in T47D cells than in MCF-7 cells. According to research, Chromolaena odorata leaf ethanol extract inhibits Bcl-2 expression, which causes MCF-7 and T47D cells to undergo apoptosis. Extract treatments on T47D showed reduced Bcl-2 expression at a dose of 135.16 μg/mL [36].

Discussion

In addition to providing therapeutic proof for some of the often used anticancer plants, the information in this article aims to provide a thorough summary or explanation of the types of processes by which plant extracts prevent cancer. Pharmacological research indicates that the traditional and customary usage of medicinal plants is associated with the existence of dynamic compounds that have anticancer potential. It has been shown that various plants may be resistant to different types of cancer cell lines, even though the emphasis of this study is breast cancer. Although several papers have identified highly active pure chemical compounds from plants, little pharmacological, phytochemical, and ethnomedicinal studies have been conducted on the majority of these species. In the future, it is imperative to conduct more clinical trials to assess the efficacy and safety of compounds derived from these plants in human populations, as well as pharmacokinetic studies to determine optimal dosing strategies.

According to this study, phytochemicals identified in Indonesian medicinal plants target breast cancer cells and stop tumor cells from proliferating and dying. With an IC_{50} value of less than 20 μg/mL, studies have shown that medicinal plant therapies, including extracts, fractions, and isolates, may prevent BC cell lines from proliferating. Acetogenin, steroid glycosides, curcumin, pinostrobin, alphitolic acid, isoxanthochymol, 4β,10α-dihydroxyaromadendrane, and 4α,10α-dihydroxyaromadendrane are among the substances that have been identified from several medicinal plants in Indonesia. In the future, these compounds have the potential to be used for breast cancer therapy [61].

Acetogenin is natural product with great potential for

future cancer therapy. Acetogenin has cytotoxic effects against multidrug-resistant human adenocarcinoma [95,96]. Moreover, acetogenin inhibits hypoxia-inducible factor-1 (*HIF-1*) activation by blocking the hypoxic induction of nuclear *HIF-1* protein and blocking hypoxic tumor angiogenesis by pressing the hypoxic induction of *HIF-1* target genes *VEGF* (vascular endothelial growth factors) and *GLUT-1* (glucose transporter-1). Inhibition of *HIF-1* activity may lead to suppression of mitochondrial respiration [97]. Acetogenin is also known to activate adenosine monophosphate-activated protein kinase (AMPK) and inhibits the signaling pathway of the mammalian target of rapamycin complex 1 (mTORC1) in colon cancer cells [98]. In addition, acetogenin bioactives also reported triggered stabilization of the p53 gene resulting in the enhancement of p53 gene expression. Acetogenin arrests the cell cycle at the G1. This is because, in the cell cycle, external interference such as the provision of anti-cancer acetogenin would be repaired completely before entering the S, G2, and M phases. In the G1 phase, there were cyclin D1 and CDKs which when joined together could activate transcriptional genes, so it can be presumed that acetogenin would suppress the expression of cyclin D1 when the expression of p53 increased. The arrest of cell cycle by the decrease of cyclin D1 may allow cells to repair the DNA damage. When the damage can not be repaired, the cell cycle can not enter the S phase [33,95].

Steroid glycosides decrease the expression of checkpoint and cyclin-dependent kinases in strophanthidine-induced cells, further confirming their effect on cell cycle arrest during the G2/M phase. The steroid glycoside class of compounds also inhibited the expression of several important proteins, including mitogen-activated protein kinase (MEK1/MAPK), Phosphoinositide 3-kinase (*PI3K*), protein kinase B (AKT), 3-ammalian Target of Rapamycin (mTOR), glycogen synthase kinase 3 (GSK3), and β-catenin, via MAPK, PI3K/AKT/mTOR, and Wnt/β-catenin. The results clearly show how the steroid glycoside class of compounds affects the expression of several important proteins involved in cell cycle arrest, apoptosis, and autophagic cell death [37,99].

Curcumin is a natural polyphenol compound and the main bioactive constituent of Indonesian spice turmeric, widely used in Indonesian medicines. Curcumin has well-known therapeutic actions, including anti-inflammatory and anti-cancer properties. Curcumin is shown to inhibit the activation of p65 (one of the NF-κB transcription factor family) in estrogen receptor (ER)-negative breast cancer cells and in prostate cancer cells. This compound also inhibits NF-κB activation pathway in the signal transduction cascade of NF-κB activation before the IκBα phosphorylation but after the point at which signals transduced by various stimuli converge. Moreover, curcumin is an inhibitor of NF-κB in a dose-dependent manner in a breast cancer cell line. Inhibiting or down-regulating NF-κB activation by curcumin leads to down-regulation of the expression of various proliferative genes and induction of apoptosis, therefore, preventing tumor cells invasion and metastasis [32,100,101].

Isoxanthochymol has anticancer properties including apoptosis, inhibition of proliferation, and metastasis. The phytochemical can be used as candidates for molecular therapy to improve the health and life expectancy of patients with breast cancer [42,102]. Based on network pharmacology, the antitumor activities of isoxanthochymol were related to the signal transducer and activator of transcription (STAT3) pathway. Isoxanthochymol suppressed the constitutive activation of the JAK2/STAT3 pathway in MCF-7 cell lines. In addition to JAK2, cytoplasmic tyrosine Src could also activate STAT3. Isoxanthochymol could inhibit the phosphorylation of Src in a dose-dependent manner. It suggested that isoxanthochymol suppressed the activation of Src together with JAK2 to modulate STAT3 phosphorylation. Blocking the STAT3 pathway could inhibit the expression of Bcl-XL and Mcl-1 and induce the apoptosis of tumor cells [102,103].

Pinostrobin, a flavonoid present in the number of medicinal plant compounds, has been shown to inhibit the growth and proliferation of a variety of cancer cells. Pinostrobin efficiently induced apoptosis in cancer cells through ROS-mediated activation of extrinsic and intrinsic signaling pathways, as well as ROS-mediated mitochondrial damage [104,105]. Pinostrobin was found to be very promotive towards modulating the cellular integrity and mitochondrial membrane potential, DNA fragmentation, and ROS production. A reduction in the cytotoxicity, ROS production, and apoptotic cell population by pinostrobin in cells pre-treated with N-acetyl cysteine (NAC), a ROS scavenger, further confirmed that generation of ROS is the key mechanism by which pinostrobin inhibits cell proliferation and induces cell death in cancer cells. In this study, the results show enhanced production of ROS, DNA fragmentation, and depolarized mitochondrial membrane potential in the pinostrobin-treated cancer cells, which could lead them to cell death through an apoptotic pathway [105,106].

Alphitolic acid is a pentacyclic triterpene constituent. The numerous reported therapeutic effects of alphitolic acid range from anti-inflammatory and antioxidant to nitric oxide (NO) inhibition and anti-cancer activities [107]. Alphitolic acid blocked Akt–NF-κB signalling, which might be related to its anti-inflammatory mechanisms. Moreover, alphitolic acid induced autophagy, as evidenced by increased expression of autophagy biomarkers Beclin 1, Atg7, and LC3B-II, and autophagosome formation. Alphitolic acid increased p53 phosphorylation/expression, accompanied by parallel decreases in the expression of the oncogenic E3 ligase MDM2, and shRNA-mediated knockdown of p53 partially rescued alphitolic acid -mediated cytotoxicity [108,109].

Phytol, phenol, and aromadendrane-type sesquiterpenoids (4β,10α-dihydroxyaromadendrane and 4α,10α-dihydroxyaromadendrane) exert anticancer effects in human cancer cells by targeting various molecular pathways and processes. These include inhibiting cell proliferation, inducing apoptosis (programmed cell death), arresting the cell cycle, and suppressing metastasis [110–112]. These compounds modulate signaling pathways such as PI3K/Akt, MAPK, STATT, and NF-κB, which contribute to their anticancer effects [110, 112, 113].

In addition to the seven Indonesian medicinal

plants (Begonia sp., Garcinia celebica, Cryptocarya pulchrinervia, Aglaia harmsiana, Syzygium aqueum, Kaempferia pandurata Roxb., Curcuma xanthorrhiza Roxb.) whose natural compounds have been identified, 56% of the 74 types of plants are still in the form of crude extracts. Plant-based crude extracts, when used directly as drugs in medicine, pose several potential risks that require cautious consideration. Plants contain a multitude of chemical compounds, and their concentrations vary, making it challenging to standardize dosages and ensure consistent therapeutic effects. Another significant concern is the potential presence of toxic or harmful compounds in plant extracts. Although many plants have traditional medicinal uses, not all of their components are safe or therapeutically beneficial. Some constituents may cause adverse effects such as toxicity or allergic reactions. Without thorough purification and identification processes, there is an increased risk of including unwanted substances in medicinal preparations. The direct use of a plant-based crude extract as a drug in medicine carries certain risks. It is important to conduct clinical trials to determine the safety, efficacy, and stability of these extracts before they can be used as crude drugs. Toxicity studies are crucial for determining the potential adverse effects of extracts.

Although the molecular mechanisms underlying the various biological activities of these compounds are not fully understood, they are likely related to cell cycle disruption, apoptosis induction, and increased efficacy of currently available cytotoxic drugs. However, with high cytotoxic activity in an in vitro study, the potential of these natural compounds is promising, making them attractive candidates for future oncology applications. Although the preclinical and clinical trials are still quite long, all of these tests must be carried out fully to understand the effectiveness of these natural compounds in cancer treatment. The journey from the laboratory to the clinic remains essential. Future efforts should focus on human clinical studies to assess the safety and efficacy of these compounds and close the large gap between preclinical discoveries and clinical applications.

Author Contribution Statement

All authors contributed equally in this study.

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Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflict of Interest

The authors declare no conflict of interest.

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