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Literature review of the cytotoxic activity of faloak (sterculia quaddrifida r.br) against t47d and mcf-7 breast cancer cells and its active compounds

Rumaldus Seran[1], Wiwin Herdwiani[2], Titik Sunarni[3]

[1,2,3]Master of Pharmacy Science, Faculty of Pharmacy, Universitas Setia Budi, Surakarta, Indonesia

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ABSTRACT

Faloak (Sterculia quadrifida R.Br) is one of the plants used by the community as a multipurpose drug. Faloak bark herb has long been used by the people of East Nusa Tenggara as a medicinal plant. Empirically, boiled water from the bark of the faloak plant is used by the people of East Nusa Tenggara as a cure for hepatitis, typhus, ulcers, and stamina recovery. The data extraction method used is narrative by grouping similar data from the literature review results according to the size of the results to be presented. The flow of the journal search is about testing the cytotoxic activity of faloak (Sterculia quadrifida R.Br) against T47D and MCF-7 breast cancer cells and the content of their active compounds. From these data, screening, journal eligibility, and monitoring of conformity with inclusion and exclusion criteria were carried out to obtain appropriate journals to conclude the cytotoxic activity of faloak. The results of a literature review showed that faloak (Sterculia quadrifida R.Br) had cytotoxic activity against T47D and MCF-7 breast cancer cells. Chemical compounds that have cytotoxic activity are alkaloids, flavonoids, terpenoids, tannins, naphthoquinone, apigenin, and puerarin. Naptaquinone derivatives 2,3-dihydro-6hydroxy-2-methylenenaphtho [1,2-b] furan-4,5-dione and 2-iminoethyl 2-(2-(1-hydroxypentan-2-yl) phenyl) acetate obtained from the extract or active fraction of faloak bark (Sterculia quadrifida R.Br) showed cytotoxic activity against T47D breast cancer cells. Apigenin compounds were found to be the most effective phytoestrogens in inhibiting the growth of breast cancer cells. Apigenin also has apoptotic effects and induces autophagy in breast cancer cells. an effective proteasome inhibitor in breast cancer cell culture and breast cancer xenografts, and puerarin can increase DUSP1 expression by increasing the expression level of miR-133a-3p in breast cancer cells.

Corresponding Author:

Rumaldus Seran,
Master of Pharmacy Science,
Faculty of Pharmacy,
Universitas Setia Budi,
Jl. Letjen Sutoyo, Mojosongo, Kec. Jebres, Kota Surakarta, Jawa Tengah, 57127, Indonesia
Email: rumaldusseran21@gmail.com

INTRODUCTION

Cancer is a general term for a large group of diseases characterized by abnormal cell growth beyond normal limits, which can then invade adjacent parts of the body or spread to other organs. Other common terms used are malignant tumors and neoplasms. Cancer can affect almost all parts of the body and has many anatomical and molecular subtypes, each of which requires specific management strategies (Septianto & Zamroni, 2023). Based on 2013 Riskesdas data, the prevalence of cancer in Indonesia reached 1.4% or around 347,000 people. Cervical cancer and breast cancer are the most prevalent types of cancer in Indonesia, accounting for 0.8% and 0.5% of the total population, respectively (Yulianti et al., 2016).

The high prevalence of cancer in Indonesia necessitates attention through preventive measures, early detection, and appropriate treatment of cancer. Cancer in more than 30% of patients can be prevented by changing behavioral risk factors, including diet, such as high body mass index, low consumption of fruits and vegetables, lack of physical activity, smoking, and excessive alcohol consumption (Rahayuwati et al., 2020). Cancer remains a global health issue, including in Indonesia. The type of cancer that is most commonly suffered and feared by women is breast cancer. In general, breast cancer affects women, with the possibility of affecting men being very small, at 1:1000 (Elmika & Adi, 2020).

Chemotherapy drugs are generally called cytostatics, which inhibit or kill all cells that are actively dividing. Normal cells that are actively dividing or multiplying are also affected, such as hair root cells, blood cells, and mouth mucosa cells. These cells are the most severely affected by the side effects of chemotherapy, which can cause hair loss, anemia, and mouth sores. Therefore, the administration of cytostatic drugs (whether medical or herbal) must be under the supervision of an experienced doctor to prevent serious side effects, and if side effects occur, they can be immediately addressed/treated. In order for normal body cells to have the opportunity to recover, chemotherapy is usually given with a 2-3 week interval before the next chemotherapy is started (Hilli, 2017). Breast cancer is one of the deadliest diseases in the world. According to data from *the World Health Organization* in 2017, deaths from breast cancer in Indonesia reached 21,287 or 1.27% of total deaths. In 2015, approximately 40,290 women were estimated to have died from breast cancer (Saragih, 2020). Breast cancer is a manifestation of malignancy that occurs in breast tissue, which can originate from the ductal epithelium to the lobules. Breast cancer does not only occur in women, but is also found in men with a frequency of about 1% (Gatsu et al., 2023).

Current research on cancer treatment is increasingly focused on testing the potential of natural compounds as chemopreventive agents that could serve as adjuncts to chemotherapy. The aim is to enhance the sensitivity of cancer cells and reduce the side effects caused by chemotherapy agents. *The selectivity index* (SI) indicates the cytotoxic selectivity of crude extracts against cancer cells compared to normal cells, calculated from the IC50 of crude samples on normal cells versus cancer cells. An SI value >3 indicates high selectivity (Mesensy & Putri, 2024).

Faloak (*Sterculia quadrifida* R.Br) is one of the plants used by the community as a multipurpose medicine. It is known to have many benefits in the fields of food, medicine, and industry. Empirically, it is used to increase stamina, cure diarrhea, treat hepatitis, relieve infections, and as an anti-cancer agent. In research, the antioxidant, antibacterial, immunomodulatory, and cytotoxic activities of this plant have begun to be reviewed. Following this research, it is hoped that insights can be gained into the utilization of natural resources to explore potential medicines from the falaok plant (Sterculia quadrifida R.Br). Much work remains to be done to ensure the safety, quality, and efficacy of the falaok plant (Sterculia quadrifida R.Br) before it can be used to treat human diseases. This study is a *Systematic Literature Review* of articles that examine the cytotoxic activity of Faloak (*Sterculia quadrifida* R.Br) against MCF-7 and T47D breast cancer cells and its active compound content. This study is expected to be a subject of study for pharmaceutical science, especially health professionals in improving the quality of breast cancer treatment.

RESEARCH METHOD

Search Method

Article searches were conducted using the *PubMed* and *Elsevier* databases. Each search in the database used several similar keyword models, including: (1) Cytotoxic activity of *Sterculia quaddrifida* R.Br, (2) Cytotoxic activity of *Sterculia quaddrifida* R.Br to MCF-7, (3) Cytotoxic activity of *Sterculia quaddrifida* R.Br to T47D. These keywords were combined with both Indonesian and English using the connector "dan/and" (and). The search strategy was limited by using several filters, including: (1) This literature review used literature published between 2013 and 2020. (2) Full text was accessible in pdf format.

Inclusion and Exclusion Criteria

The inclusion criteria in this journal search are: (1) The data used is only related to the cytotoxic activity of faloak bark extract on MCF-7 and T47D breast cancer cells. (2) Indonesian and English languages. (3) International journals, *full text*. (4) Journals indexed *in PubMed* and *Elsevier*. The exclusion criteria for this journal search are: (1) Journal *papers* classified as *systematic reviews.* (2) Journal *papers* that are the same or duplicates. (3) Journal *papers* outside the scope of the research.

Study Selection

Initial searches were conducted through *PubMed* and *Elsevier,* using the keywords (1) Cytotoxic activity of *Sterculia quaddrifida* R.Br, (2) Cytotoxic activity of *Sterculia quaddrifida* R.Br to MCF-7, (3) Cytotoxic activity of *Sterculia quaddrifida* R.Br to T47D. As many articles as possible were collected, then 10 journals were selected for review with restrictions according to the inclusion criteria and search strategy, resulting in several suitable articles.

Data Extraction

Extraction or grouping of article data was presented based on previous research results related to the cytotoxic activity of extracts, fractions, and isolates against MCF-7 and T47D cancer cells and the chemical content *of Sterculia quaddrifida* R. Br.

Data Analysis

Data analysis in this study was conducted by carefully reading the abstracts and *full-text* journal *articles* resulting from the inclusion, and the results were in the form of extracted data. The collected data were then compared for similarities and differences and discussed to draw conclusions.

Research Flow

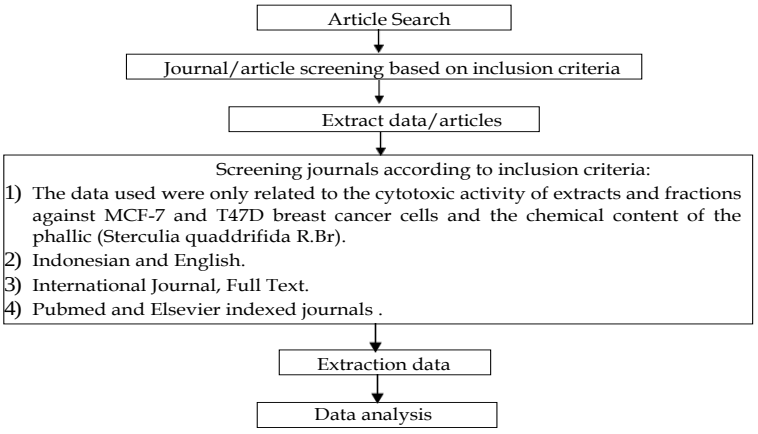

Figure 1. Research flow diagram

RESULTS AND DISCUSSIONS

This *literature review* was conducted to determine the cytotoxic activity of extracts and fractions, as well as the chemical content of faloak (*Sterculia quaddrifida* R.Br) on MCF-7 and T47D breast cancer cells using existing literature collection techniques to answer the objectives of the literature review that have been stated. All journals were international and national journals searched on the *Pubmed and Elsevier* portals by typing the keywords cytotoxic test of faloak bark (*Sterculia quaddrifida* R.Br), extract, fraction of faloak bark (*Sterculia quaddrifida* R.Br), cytotoxic effects of faloak bark (*Sterculia quaddrifida* R.Br) on MCF-7 and T47D breast cancer cells. The journals were then analyzed using *critical appraisal* analysis. The following is a table of *critical appraisal* analysis of these journals:

Cytotoxic Activity of Faloak Bark (*Sterculia quaddrifida* R. Br)

Table 1. Results of the search for the cytotoxic activity of faloak bark (*Sterculia quaddrifida* R. Br) against MCF-7 and T47D cancer cells

No	Test Material	Methods and parameters	Research Results	References
1	Extracts and fractions of faloak bark (*Sterculia quaddrifida* R.Br)	MTT Assay on T47D cancer cells with IC50 observation parameters.	Fraction 4, IC50 = 21.89 µg/mL	(Rollando & Siswadi, 2016)
2.	Ethanol extract, n-hexane fraction, ethyl acetate fraction, and water fraction of faloak bark (*Sterculia quaddrifida* R.Br)	MTT Assay on T47D and MCF-7 cancer cells with IC50 as the observation parameter.	1. Ethanol extract IC50 = 157.4 µg/mL (T47D) IC50 = 24.9 µg/mL (MCF-7) 2. Ethyl acetate fraction (Most active) IC50 = 9.56 µg/mL (T47D) IC50 = 7.62 µg/mL (MCF-7)	(Hertiani et al., 2019)
3.	Ethyl acetate fraction of faloak bark (*Sterculia quaddrifida* R. Br)	MTT Assay on T47D breast cancer cells with IC50 observation parameters.	The ethyl acetate fraction caused cell accumulation in the S phase (27.43%) in T47D breast cancer cells and was able to induce apoptosis.	(Rollando & Prilianti, 2017)

Chemical Composition of Faloak (*Sterculia quaddrifida* R. Br)

Table 2. Test materials and chemical composition of faloak plant extract (*sterculia quaddrifida* R. Br)

No	Test Material	Chemical Content	References
1	Ethanol extract and ethyl acetate fraction of faloak bark	Total phenolics and flavonoids	(Hertiani et al., 2019)
2	Acetone, ethyl acetate, methanol, and n-hexane extracts of faloak bark	Flavonoids, phenolics, and terpenoids.	(Rollando & Siswadi, 2016)
3	Extracts and fractions of faloak plant bark	Flavonoids, phenolics, tannins, and terpenoids	(Rollando & Prilianti, 2017)
4	Extract fractions and isolation of faloak bark	2-iminoethyl 2-(1-hydroxypentan-2-yl) phenyl) acetate	(Rollando et al., 2018)
5	Extraction and isolation of faloak bark	Naptokuinone 2,3-dihydro-6-hydroxy-2-methylenenaphtho[1,2-b]furan-4,5-dione	(Rollando & Alfanaar, 2017)
6	Extracts and fractions from the bark, seeds, and leaves of the faloak plant	5,7,8-tetrahydroxy-4'-methoxyflavone-8-O-β-D-glucoside, apigenin-6,8-di-C-β-D-glucoside, puerarin, 5,7,8-tetrahydroxy-3',4'-dimethoxyflavone, 5,7,8-tetrahydroxy-4'-methoxyflavone	(Rollando et al., 2020)

Cytotoxic activity of faloak (*Sterculia quaddrifida* R.Br) plant compounds against breast cancer cells.

Table 3. Cytotoxic activity of faloak bark (*Sterculia quaddrifida* R.Br.) chemical compounds against breast cancer cells and P53

No	Test material	Methods and parameters	Research Results	References
1	Naptakuinone derivatives isolated from the bark of faloak (*Sterculia quaddrifida* R.Br)	MTT Assay on T47D cancer cells with IC50 observation parameters.	Naptakuinone derivative compound 2,3-dihydro-6-hydroxy-2-methylenenaphtho[1,2-b]furan-4,5-dione. IC50 9.88 µg/mL (T47D)	(Rollando & Alfanaar, 2017)
2.	Isolates of 2 naptakuinone derivatives from the bark of faloak (*Sterculia quaddrifida* R.Br)	MTT Assay on T47D cancer cells with IC50 observation parameters.	Compound 2-iminoethyl 2-(2-(1-hydroxypentan-2-yl)phenyl) acetate. IC50 7.12 µg/mL (T47D)	(Rollando et al., 2018)
3.	Apigenin	Breast cancer MDA-MB-231 cell cultures and xenografts were treated with apigenin, followed by measurement of reduced cell viability/proliferation, proteasome inhibition proteasome inhibition, and induction of apoptosis	Doses of 25 µM, 50 µM, 75 µM and 100 µM apigenin inhibited cell viability/proliferation by by 12%, 27%, 42%, and 49%	(Chen et al., 2007)
4.	Apigenin	immunoblot, transfection with luciferase reporter vector, and MTT test	apigenin: at a concentration of 50 µM, 20% of MCF-7 cells compared to the control caused 60% cell death in SKBR3 (3-day incubation with phytoestrogen)	(Scherbakov & Andreeva, 2015)
5.	Apigenin	MTT assay of human breast cancer cells T47D and MDA-MB-231 and clonogenic assay. Flow cytometry, Western blot analysis	MDA-MB-231 and T47D cells were treated with apigenin at concentrations of 0, 10, 20, 40, and 80 µM,	(Cao et al., 2013)
6.	Puerarin	Cell viability assay on HCC38 cells using the Kit-8 Cell Counting assay and flow cytometry, Western blotting, reporter gene assay luciferase	puerarin (0, 10, 20, and 40 µM). With 20 µM puerarin, the control miR-133a-3p, puerarin 20 µM + miR-133a-3p	(Li et al., 2019)
7.	1,4-naphthoquinone	Sulforhodamine B (SRB) cell viability assay, Muse Cell Analyzer, flowcytometric.	MDA-MB-231 cells (12.5 µM) for 12 and 24 hours	(Karaka\cs et al., 2019)

Discussion

Cytotoxicity tests are generally performed to determine the potential for cell growth inhibition due to extract treatment and to determine the sample concentration that can inhibit cell growth by 50% . Cytotoxicity tests in this study are expressed in IC50 parameters. The IC50 value is the concentration that results in 50% cell growth inhibition. Cell viability can be calculated using several staining methods and measured using Multiwell Scanning Spectrophotometers (ELISA Reader) (Susanty et al., 2018). One method for measuring cell viability is the MTT assay. In general, staining methods use the principle of colorimetry, which uses several color changes as endpoints for quantifying the number of cells. The requirements that must be met for cytotoxicity testing include that the test must be able to produce a dose-response curve with a low level of difference, the response criteria must show a linear relationship with the number of cells, and the information

obtained from the dose-response curve must be consistent with the effects that appear in vitro. One of the methods commonly used to determine the number of cells is the MTT method.

The principle of the MTT method is the reduction of the yellow tetrazolium salt MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) by the reductase system. Tetrazolium succinate, which is part of the respiratory chain in the mitochondria of living cells, forms purple, water-insoluble formazan crystals. The addition of a stopper reagent (detergent) dissolves these colored crystals, which are then measured for absorbance using an ELISA reader. The intensity of the purple color formed is proportional to the number of living cells. Thus, if the intensity of the purple color is greater, it means that the number of living cells is greater (Johan, 2011). The interaction of the ethyl acetate fraction with breast cancer cells was observed using a cytotoxicity test with concentrations below IC50 with n-hexane fraction, ethyl acetate fraction, and water fraction treatments. The focus of this study was on the classification of cytotoxicity effects with the condition that the viability percentage of breast cancer cells was less than 50%. The methanolic extract of faloak bark contains naphthoquinone-derived flavonoids that have a mechanism of action on breast cells, whereby naphthoquinone significantly inhibits breast cell proliferation. The ethyl acetate fraction can effectively suppress breast cell growth by stimulating the necroptosis pathway. Necroptosis plays an important role in inhibiting breast cell proliferation and viability (Khorsandi et al., 2017).

Apoptosis was performed to determine the mechanism of cell death through the apoptotic or necrotic pathway. Apoptosis was detected using the FASC Calibur device with the *CellQuest* program and the Annexin V Fluos method. The *flow cytometry* method only detects one specific characteristic of the apoptotic process. This method can measure specific cell populations undergoing apoptosis, necrosis, and cells that are still alive. Breast cancer cells entering the apoptosis phase show asymmetric loss of phospholipids, with PS opening on the outside. Annexin V binds to the negative charge of PS. In necrotic cells, the cells break down and the cell contents are released into the environment. Then, PI binds to DNA. Thus, the bond between PI and DNA can be detected by *flow cytometry*. Faloak bark extract induces breast cancer cells through the necrosis pathway. However, it should be noted that there is a small population of cells undergoing apoptosis, so it is necessary to optimize the concentration of faloak bark extract so that the population of cells undergoing apoptosis is more optimal.

Chemical Content of Faloak (*Sterculia quaddrifida* R. Br)

Based on Table 2, many studies have been conducted to identify secondary metabolites in faloak plants (*Sterculia quaddrifida* R.Br), such as leaves, seeds, and bark. Research conducted by states that the ethyl acetate fraction of faloak bark is used as an herbal chemopreventive agent for cancer. Through chemical compound group testing, stated that acetone, ethyl acetate, methanol, and n-hexane extracts from the bark of the faloak plant contain flavonoids, phenolics, and terpenoids. The bark fraction of faloak contains saponins and triterpenoids (Rollando et al., 2018) . It has been reported that several steroids and triterpenoids such as lupeol, lupenone, and betulinic acid (pentacyclic triterpene); steroids such as sitosterol, stigmasterol, and lupenone. Some flavonoid isolates, namely luteolin, quercetin, and fisetin, can reduce phagocytosis. According to the cytotoxicity test results, the ethyl acetate fraction was the most active in stimulating macrophage phagocytosis in mice. Previous research has reported the isolation of naphthoquinone compounds from the ethyl acetate fraction, which showed potential effects on MCF-7 cells (Rollando & Prilianti, 2017). The isolation of active compounds from the ethanol extract of faloak bark (*Sterculia quadrifida* R.Br) has been successfully carried out. The active compound is a naphthoquinone derivative, namely 2,3-dihydro-6-hydroxy-2-methylenenaphtha [1,2b]furan-4,5-dione. This compound is active as an anticancer agent against MCF-7 breast cancer cells with an IC50 of 9.88 µg.

Overall, it can be said that faloak bark extract has the potential to be developed as a chemotherapeutic agent. Faloak bark extract at an optimal dose is capable of producing a cytotoxic effect on breast cancer cells. Given the great potential of faloak bark extract, further development is needed regarding molecular mechanisms such as observing the proliferation kinetics that mediate the effects of faloak bark extract. Furthermore, cytotoxicity testing against normal cells, such as Vero cells, is needed to determine the toxicity of faloak bark extract.

Apigenin can inhibit cell viability/proliferation and activate caspase-3/caspase-7 activity in MDA-MB-231 breast cancer cells in a dose-dependent manner. Di Chen *et al* previously showed that Jurkat T leukemia cells exposed to increasing concentrations of apigenin (up to 50 µM) experienced up to 80% cell death after 24 hours of treatment. In this study, Di Chen *et al.* first investigated the dose-dependent effects (25, 50, 75, or 100 µM) of apigenin on the highly metastatic and invasive human breast cancer cell line, MDA-MB-231. MTT assay results revealed that apigenin inhibited cell viability and potentially proliferation after 24 hours of treatment in a dose-dependent manner.

Compared to the DMSO control, treatment with 25 µM, 50 µM, 75 µM, and 100 µM apigenin inhibited cell viability/proliferation by 12%, 27%, 42%, and 49%, respectively. Furthermore, dose-dependent activation of caspase-3/caspase-7 was observed in the same experiment, with an almost fivefold increase in cells treated at the highest concentration. In addition, morphological changes were observed after increasing the apigenin dose in the same experiment. Compared to the DMSO control, the cells became elongated, lost their morphological characteristics, and possibly showed cellular stress. Inhibition of proteasomal chymotrypsin-like activity, but not trypsin-like activity, has been shown to be associated with the induction of apoptosis in cancer cells. To investigate whether proteasomal inhibition is associated with the induction of apoptosis, the presence of cleaved PARP was examined. Apoptosis-specific cleaved PARP was detected in cells treated with 50 µM apigenin and higher concentrations. These results indicate that apigenin is capable of inhibiting proteasomal chymotrypsin-like activity, resulting in the induction of apoptosis in human breast cancer MDA-MB-231 cells.

AM Scherbakov and OE Andreeva reported that the flavone apigenin exhibits high antiproliferative activity in cells with various estrogen receptor statuses. At high doses, apigenin was found to prevent estrogen receptor activation by 17β-estradiol and cause inhibition of HER2/neu expression, accompanied by PARP degradation in HER2-positive breast cancer cells. Other targets of apigenin were identified in breast cancer cells, including proteins that support tumor growth and survival: PI3K/Akt, STAT3, NF-κB, p53, p21, JAK3, cyclin D1, D3, and Cdk4, and VEGF. It turns out that apigenin is a multi-target compound that triggers breast cancer cell death through the inhibition of tyrosine kinase receptors, decreased growth factor expression, p53 activation, and suppression of transcription factors. In 2008, a phase II clinical trial (NCT00609310) of a drug containing 20 mg of apigenin and 20 mg of epigallocatechin gallate in patients with colorectal cancer was registered in the ClinicalTrials.gov database. The first batch of data from this study, concerning changes in disease recurrence rates in patients treated with this phytoestrogen mixture, is expected in 2016. No other clinical trials of apigenin (as an antitumor agent) are currently registered on ClinicalTrials.gov.

Further investigation of the antitumor activity of apigenin and its synthetic derivatives is promising, especially in relation to HER2-positive breast tumors. In this study, Xuchen Cao *et al* found that apigenin effectively inhibited breast cancer cell growth by inducing apoptosis. Autophagy was also determined to occur concurrently with apoptosis in breast cancer cells. The aim of this study was to uncover the role of autophagy in the apoptosis process and to elucidate the crosstalk between autophagy and apoptosis, which may be a new strategy for breast cancer therapy. To evaluate the effect of apigenin on apoptosis, fluorescence microscopy, flowcytometric and Western blot analyses were performed, revealing that apigenin-induced apoptosis in breast cancer cells in a dose- and time-dependent manner. There is growing evidence that autophagy can

provide a protective response in cancer cells under unfavorable conditions, such as hypoxia and nutrient deprivation. However, it has also been reported that autophagy is triggered in response to various anticancer agents, including As2O3, tamoxifen, and epirubicin, in several types of cancer.

The results of this study indicate that apigenin can induce autophagy in breast cancer cells, as evidenced by the formation of autophagic vacuoles and increased LC3-II levels. Flow cytometry further showed that the autophagy-inducing effect of apigenin occurred in a dose- and time-dependent manner. Apigenin, a natural plant flavone, can inhibit the proliferation of T47D and MDA-MB-231 breast cancer cells by inducing apoptosis. In addition, autophagy induced by apigenin also increased in parallel with apoptosis. Inhibition of autophagy by 3-MA enhanced apigenin-induced apoptosis. Therefore, the combination of apigenin and autophagy inhibition is a new and promising strategy for breast cancer therapy.

Because puerarin has the potential to suppress tumor cell growth, research has focused on understanding the biological activity of puerarin. Furthermore, the mechanism of puerarin as an anticancer drug may involve the induction of tumor suppressor genes or the inhibition of oncogenes. These results show that the viability of HCC38 breast cancer cells is suppressed by puerarin. Additionally, HCC38 apoptosis is promoted, and these findings provide a basis for further investigation of puerarin's effects on breast cancer. In this study, puerarin promotes the expression of tumor suppressor genes miR-133a-3p and DUSP1, suggesting that puerarin may influence this pathway to exert antitumor effects. Furthermore, based on bioinformatic analysis, interactions between the miR-133a-3p and DUSP1 genes were identified based on nucleotide sequences. The expression of the DUSP1 gene is promoted by increased regulation of miR-133a-3p. Xiao et al. showed that miRNAs can increase gene expression by targeting enhancers. DUSPs are a family of proteins that function as negative regulators of MAPK activity in mammalian cells.

A previous study suggested that silencing DUSP1 promotes the release of pro-inflammatory cytokines by activating the MAPK signaling pathway. This study identified that upregulation of DUSP1 expression leads to increased levels of p-p38 MAPK protein expression. Collectively, this study identified that puerarin decreases HCC38 cell viability and increases apoptosis. The underlying mechanism of puerarin involves the upregulation of miR-133a-3p expression. Specifically, the upregulation of miR-133a-3p increases the expression level of DUSP1, leading to a decrease in the expression level of p-p38 protein. The impact of the downstream genes of the MAPK pathway has not been investigated, which is a limitation of this study, and additional experiments are needed to address this aspect. The current results investigate the molecular mechanisms of puerarin, a drug that could be used in the future to improve the quality of life of breast cancer patients.

Based on research (Khorsandi et al., 2017), it is suggested that MDA-MB-231 cells undergo mitochondria-dependent apoptosis after treatment with these compounds. Quinone-based drugs (such as doxorubicin, mitoxantrone, streptonigrin, and mitomycin C) have been widely used in the treatment of breast cancer. The mechanism of action of these drugs is based on DNA targeting (DNA intercalation, crosslinking, strand break, etc.) (Satyarsa et al., 2020). As we stated earlier, superoxide radical anions and semiquinone can also cause DNA strand breaks. Phosphorylation of H2AX at serine 139 is known as a marker of DNA damage. The results of this study indicate that these compounds cause an increase in H2AX phosphorylation (DNA damage) in MDA-MB-231 cells. Overall, these findings suggest that these compounds enhance mitochondrial apoptosis in triple-negative breast cancer cells. Given the challenges in treating TNBC, further investigation is needed to evaluate the detailed mechanism of action.

The bark of faloak is suspected to contain naphthoquinone compounds that have been proven to be cytotoxic in T47D and MCF-7 cells. Conducted cytotoxicity tests on T47D and MCF-7 cells using ethanol extract, n-hexane fraction, ethyl acetate, and water from faloak bark (*Sterculia quaddrifida* R.Br) methanolic bark of faloak with IC50 values of Ethanol extract IC50 = 157.4 µg/mL (T47D) IC50 = 24.9 µg/mL (MCF-7) and Ethyl acetate fraction (Most active) IC50 = 9.56 µg/mL.

(T47D) IC50 = 7.62 µg/mL (MCF-7). Cytotoxicity testing of faloak methanolic extract has been conducted on MCF7 cancer cells, showing strong cytotoxic effects. Faloak bark extract is able to inhibit proliferation, invasion, and cancer growth, as it is suspected that there is a compound that plays a role, namely naphthoquinone.

Research conducted by (Alfanaar & others, 2017) states that the methanolic extract of faloak bark contains flavonoid glycoside naphthoquinone. This compound is known to induce cell growth inhibition through the inhibition of DNA topoisomerase I/II activity, modulation *of signaling pathways*, decreased expression of Bcl-2 and Bcl-XL genes, increased expression of Bax and Bak genes, and activation of endonuclease (Safitri et al., 2020). Naphthoquinone has the ability to induce cell growth inhibition in colon cancer cells Caco-2 and HT-29, as well as leukemia cells HL-60, by stimulating the release of cytochrome c from mitochondria.

CONCLUSION

Based on data from several journals collected in this study and its interpretation, it can be concluded that faloak (*Sterculia quadrifida* R.Br) has cytotoxic activity against MCF-7 and T47D breast cancer cells. The active compounds contained in faloak, including naphthoquinone derivatives, apigenin, and puerarin, have cytotoxic activity against breast cancer cells.

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