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Systematic Literature Review Potential of Sappan Wood Plants (*Caesalpinia sappan L.)* As Anticancer

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ABSTRACT

Sappan wood (Caesalpinia sappan L.) is one of the plants that is known as having an effect as anticancer. The use of sappan wood as an anticancer scientifically has done many research but it has not delivered holistically. Furthermore, a systematic literature review is needed in order to get a wider understanding and the data that is more accurate so that it can be a reference for the researcher in developing the new medicine for anticancer. This literature research is having a purpose to determine the sappan wood's compound that has activity as an anticancer, to determine the prediction of anticancer activity on sappan wood in silico method, and the activities of anticancer in vitro and in vivo studies and also to determine how the mechanism is in order to develop the compounds as an anticancer. This research is using systematic literature review and the data are obtained by PRISMA method ((Preffered Reporting Items for Systematic reviews and Meta-analyses). The article searching method in this article is using database in Google Scholar, ScienceDirect, SpringerLink, and PubMed which is then being analysed so that the researcher obtain 27 suitable articles. The analysis result exhibit that the compound inside sappan wood that has activity as an anticancer are brazilin, brazilein, sappanchalcone, 3-deoxysappanchalcone, caesalpiniaphenol G, dan caesalpiniaphenol H. Sappan wood is proven having a prediction concerning anticancer activities in silico, and the anticancer activities in vitro and in vivo through several mechanism. They are apoptosis induction, inhibition of the cell cycle, antimetastasis, antiproliferative, inhibition of HO-1 expression, and inhibition of BAF.

Key words: Anticancer, Caesalpinia sappan L., Systematic Literature Review

INTRODUCTION

Cancer is a non-communicable disease caused by the presence of abnormal cells that experience uncontrolled cell division and the ability of cells to attack other biological tissues, either by direct growth in adjacent tissues or by moving cells to distant places (Pratiwi et al, 2017). Based ondata from Globocan, International Agency for Research on Cancer (IARC) mentioned in the last 5 years, the prevalence of

cancer worldwidereached 50,550,287 cases.Whereasin Indonesia alone, the prevalence of cancerin the last 5 years reached 946,088 cases. Where in 2020 the number of new cases in Indonesia has reached 396,914 cases with a death rate of 234,511 cases. Medical cancer treatment is usually carried out with several treatment measures such as surgery, chemotherapy, radiotherapy, and hormonal therapy. However, some of them can trigger side effects that are unintentionally harmful to the patient's welfare and health (Agustin, 2021). The many side effects caused and the relatively expensive cost of conventional medicine, has made patients take the initiative to return to using natural ingredients as alternative complementary medicines. This is indicated by an increase in the prevalence of the use of traditional, complementary and alternative medicine by 40% (Horneber et al., 2012).

Sappan wood (Caesalpinia sappan L.) is a plant in the caesalpiniaceae familyempirically it is known to have many healing properties and is often consumed by the public as a health drink. Sappan wood is also used extensively in traditional medicine. Several studies reveal the potential effects ofCaesalpinia sappan L. and its compounds are used in the treatment of cancer. Main contentBrazil andbrazilein isolated from sappan wood can inhibit the growth of cancer cells by inducing apoptosis. Compound brazilein also inhibits cancer cell migration, where migration and invasion are important processes in the early stages of metastasis. So, Caesalpinia sappan L. demonstrated promising anticancer agents targeted at inhibition of proliferation and metastasis (Jenie et al., 2017).

Currently there have been many discoveries and developments of new cancer drugs. In the drug development process, of course, testing must be carried out. As for some of the tests carried out, namely test in silico, in vitro and live. Based on the explanation above, it is necessary to do itsystematic literstur review related to the development of drugs from natural ingredients, namely the sappan wood plant (Caesalpinia sappan L.) as a cancer therapy.Systematic literatur review Related to the anticancer potential of sappan wood, it is important to do this, because in the development of new drugs for cancer, a broader level of understanding and more accurate data is needed from various studies by identifying, studying and interpreting which compounds contained in sappan wood have the potential as anticancer, prediction of anticancer activity in assays in silico, and anticancer activity in the assay in vitro and liveas well as how the mechanism is as anticancer so that it can be used as a strong reference for researchers in developing new drugs for various types of cancer.

METHODS

This study used the Systematic Literature Review (SLR) method by collecting data using the PRISMA method(Preffered Reporting Items For Systematic reviews and Meta-analyses). The inclusion criteria in this study were articles in the form ofOriginal / research article and in full text. Published articles spanning 2011-2021 using Indonesian and English. This article contains compounds in sappan wood that have anticancer activity, predictions of anticancer activity in sappan woodin silico, and anticancer activity in the assayin vitro andlive and its mechanism as anticancer. Data sources or databases used as a place to search for articles are Google Scholar, ScienceDirect, SpringerLink, and PubMed.

The first step is to visit the database by writing the keywords "Caesalpinia sappan" and "anticancer" and produced a total of 5.020 articles. Then identification of the language and year of publication was carried out so that the remaining 2.378 articles were obtained. Once it's done screening articles based on duplication of articles and research article, then the results of the remaining articles were 1.157 findings. Further screening was carried out by looking at topic relevance or topic suitability by looking at the abstracts in the articles, so the remaining results were 58 articles. Research articles that have been in screening then filtered based on eligibility

by looking at the journal index and the completeness of the data. The findings of research articles that have fulfilled the completeness and feasibility of data are 27 articles. Furthermore, data synthesis was carried out using the metasynthesis method. This method is carried out by grouping filtered data which is then studied and analyzed in depth so that conclusions can be obtained that can answer the objectives.

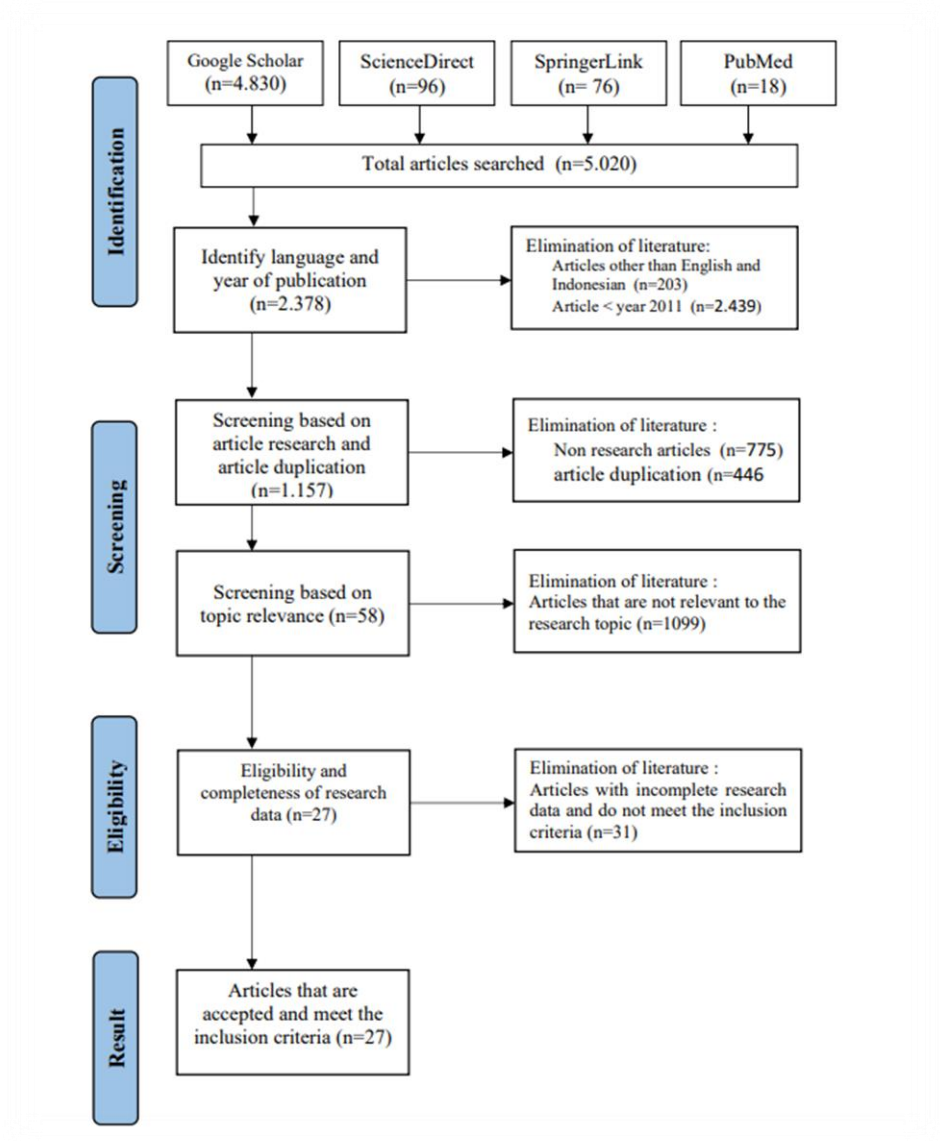

Figure 1. PRISMA Flow Diagram

RESULT AND DISCUSSION

Based on the results of the literature search that has been carried out, a total of 27 articles were obtained, with details on the Google Scholar database with 17 findings, 3 findings in Sciencedirect, 1 finding in Springerlink, and 6 findings in Pubmed. Furthermore, data synthesis

was carried out by grouping the data in tabular form which was then studied and analyzed. The following is a table of research results based on PICO analysis.

Table 1. Results of Systematic Literature Review of Sappan wood (Casealpinnia sappan) Based on PICO Analysis

No	Researcher	Research title	Research methods	Population	Intervention	Control	Outcome
1.	Rachmady et al., 2017	Antiproliferative Effect of Sappan Heartwood Ethanolic Extract (*Caesalpinia sappan L.*) on HER2-Positive Breast Cancer Cells	- *In vitro* use*MTT Assay dan* Immunofluoresensi - *In silico* use*molecular docking*	Ethanol extract	- Cytotoxic activity - HER2 inhibitory activity	lapatinib in trials*in silico* with a value of -120	- IC50 25 µg/mL on MCF-7/ HER2 - Mechanism of inhibition of HER2 protein. - *rerank score Brazil, Brazil* on HER-2 is -77; -73
2.	Tao et al., 2011	Brazilein overcame ABCB1-mediated multidrug resistance in human leukaemia K562/AO2 cells	*In vitro* use*MTT Assay dan flow cytometry*	Brazilin compound isolate	- Cytotoxic activity - Analysis of apoptosis induction	-	- IC50 5,45 ± 0,36 and 5,62 ± 0,43 µ.mol/L on K562 and K562/AO2 - Mechanism of induction of apoptosis
3.	Tao et al., 2013	Brazilein, a compound isolated from *Caesalpinia sappan Linn.*, induced growth inhibition in breast cancer cells via involvement of GSK-3b/b-Catenin/cyclin D1 pathway	*In vitro* use *MTT Assay, flow cytometry dan Western blot*	Brazillein compound isolate	- Cytotoxic activity - Cell cycle analysis and involvement of GSK-3b/b-*catenin*	-	- IC50 7.23 ± 0.24 µmol/L against MCF-7 - G1 phase cell cycle inhibition by decreasing Akt/GSK-3b/b-catenin.
4.	Kim et al., 2012	Brazilin Induces Apoptosis and G2/M Arrest via Inactivation of Histone Deacetylase in Multiple Myeloma	*In vitro* using MTT*assay,* HDAC assay kit, *flow cytometry*, and TUNEL	Brazilin compound isolate	- Cytotoxic activity - Analysis of HDAC activity,	-	- The mechanism of HDAC inactivation in U266 cells is through induction of apoptosis and inhibition of the

		U266 Cells			apoptosis induction and cell cycle		G2/M phase of the cell cycle
5.	Lee et al., 2013	Brazilin Inhibits Growth and Induces Apoptosis in Human Glioblastoma Cells	*In vitro* using MTT Assay, and western blot.	Brazilin compound isolate	- Cell proliferation analysis - Analysis of apoptosis induction	-	- Mechanism of induction of apoptosis of U87 cell caspases pathway.
6.	Hung et al., 2013	Cytotoxic Activity of New Phenolic Compounds from Vietnamese Caesalpinia sappan	*In vitro* using the MTT Assay,*dan DNA laddering assay*	Isolates of caesalpiniaphenol G and caesalpiniaphenol H compounds	- Cytotoxic activity - Analysis of apoptosis induction	- Adryamycin(IC50 3.0 + 0.4 µg/mL in HL-60 cells, (4.9 + 0.4) in HeLa cells, (2.4 + 0.2) in mcf-7 cells and (2, 8 + 0.3) in the LLC cell.	- Caesalpiniaphenol G (a) IC50 16,7+ 2,2 µg/mL on HL-60 cells (b) IC50 28,1+ 3,6 µg/mL on HeLa cells (c) IC50 >100 µg/mL on MCF-7 and LLC cells - caesalpiniaphenol H (a) IC50 22,5 + 5,1 µg/mL on HL-60 cells (b) IC50 39,2 + 2,0 µg/mL on HeLa cells (c) IC50 >100 µg/mL on MCF-7 cells and IC50 42,5 + 5,1µg/mL. on the LLC cell - Caesalpiniaphenol G inhibits HL-60 cells by

							inducing apoptosis.
7.	Jenie et al., 2017	Cytotoxic and Antimetastasis Effect of Ethyl Acetate Fraction from *Caesalpinia sappan L.* on MCF-7/HER2 Cells	*In vitro uses*assay MTT Assay, Flowcytometry, and*Zymography Gelatin*	Ethyl acetate fraction	- Cytotoxic activity - Cell cycle analysis, induction of apoptosis and activity of MMP-9, MMP2 and Rac1	-	- IC50 33,5±3,1 µg/mL on MCF-7/HER2 - Mechanism of induction of apoptosis, inhibition of cell cycle S phase and G2/M phase, regulation of MMP9, MMP2, and Rac1 expression
8.	Tirtanir mala et al., 2015	Cytotoxic and Apoptotic-inducing Effect of Fraction Containing Brazilein from *Caesalpinia sappan L.* and Cisplatin on T47D Cell Lines	*In vitro uses*MTT Assay test, and*flowcytometry*	Fraction containin g brazilein	- Cytotoxic activity by MTT assay - Analysis of apoptosis induction	Cisplatin (IC50 16 M)	- IC50 68 µg/mL on T47D cell - Mechanism of induction of apoptosis.
9.	Utomo et al., 2018	Enhancement of Cytotoxicity and Apoptosis Induction of Doxorubicin by Brazilein Containing Fraction of Sappan (*Caesalpinia sappan L.*) on T47D Cells	- *In vitro* using MTT assay and Flowcytometr y - *in silico* use*molecular docking*	Fraction containin g brazilein	- Cytotoxic activity - Analysis of apoptosis induction	Doxorubicin (IC50 403 nM)	- IC50 68 µg/mLpada sel T47D - Mechanism of induction of apoptosis - Binds to bcl-2 in silico
10.	Husnaa et al., 2017	Ethyl Acetate Fraction of *Caesalpinia sappan L.* Enhances Cisplatin's Cytotoxicity on HeLa Cells via G1 and S Arrest through p53	- *In vitro* using MTT assay and Flowcytometr y	Ethyl acetate fraction	- Cytotoxic activity - Cell cycle analysis and induction of	Cisplatin (IC50 16 M)	- IC50 65±1,5 µg/mL on HeLa cells - The mechanism of cell cycle inhibition is via p53.

		Expression			apoptosis		
11.	Rivanti et al., 2017	Heartwood of Sappan (*Caesalpinia sappan L.*) Ethanolic Extract Show Selective Cytotoxic Activities on T47D and Widr Cells But not on Hela Cells	*In vitro* use*MTT assay*	Ethanol extract	- Cytotoxic activity	-	- IC50 36 µg/mL on T47D cell - IC50 30 µg/mL on WiDr cells - IC50 327 µg/mL on HeLa cells
12.	Hung et al., 2014	Methanol extract from *Vietnamese Caesalpinia sappan* induces apoptosis in HeLa cells	*In vitro* using MTT assay and DNA laddering	Methanol extract	- Cytotoxic activity - Analysis of DNA fragmentation and Caspase-3	Camptothecin (IC50 3.4 ± 0.2)	- IC50 26,5 ± 3,2 µg/mL on HeLa cells - The mechanism of induction of apoptosis through caspase-3.
13.	Ngernnak et al., 2018	Phytochemical And Cytotoxic Investigations Of The Heartwood of *Caesalpinia Sappan L*in.	*In vitro* using the MTT assay	Brazilin compound isolate	- Cytotoxic activity by MTT assay	-	- IC50 13.30 ± 0.49 and 12.24 ± 1.08 g/ml, in KG1 and KG1a cells
14.	Haryanti et al., 2018	Cytotoxic and MMPs inhibitory activities of Sappan Wood (Caesalpinia sappan L.): various extracts on 4T1 breast cancer cell line	*In vitro* using the MTT assay*dan Zymography Gelatin*	Ethanol extract	- Cytotoxic activity - MMP-9 inhibitory activity	-	- IC50 13,1 µg/ml. on 4T1 cells - Mechanism of inhibition of MMP-9 expression
15.	Nurzijah et al., 2012	A cup (*Caesalpinia sappan L.*) Heartwood Ethanolic Extract Shows Activity as Doxorubicin	*In vitro* using the MTT assay and *flowcytometry*	Ethanol extract	- Cytotoxic activity by MTT assay - Analysis of apoptosis	-	- IC50 35 µg/ml on cell T47D - Mechanism of induction of apoptosis

		Cochemotherapeutic Agent by Apoptotis Induction on T47D Breast Cancer Cells			induction		
16.	Kwak et al., 2021	The 3-deoxysappanchalcone induces ROS-mediated apoptosis and cell cycle arrest via JNK/p38 MAPKs signaling pathway in human esophageal cancer cells	*In vitro* using the MTT assay and *flowcytometry*	3-deoxysappanchalcone compound isolate	- Cytotoxic activity - Analysis of apoptosis induction and cell cycle	-	- IC50 19.8 µ.mol/L on a KYSE 30 ESCC cell - 12.2 µ.mol/L on a KYSE 410 ESCC cell - Mechanisms of apoptosis induction and cell cycle inhibition
17.	Haryanti et al., 2016	The Synergistic Effect of Doxorubicin and Ethanolic Extracts of *Caesalpinia sappan L*. Wood and Ficus septica Burm. f. Leaves on Viability, Cell Cycle Progression, and Apoptosis Induction of MCF7 Cells	*In vitro* using the MTT assay and *flowcytometry*	Ethanol extract	- Cytotoxic activity - Analysis of apoptosis induction and cell cycle	-	- IC50 32 µg/mL on MCF-7 cells - Mechanisms of induction of apoptosis and inhibition of cell cycle phases G1 and G2/M.
18.	Handayani et al., 2016	Brazilein in Combination with Cisplatin Inhibit Proliferation and Migration on Highly Metastatic Cancer Cells, 4T1	*In vitro* using the MTT assay,*flowcytometry*, and*Zymography Gelatin*	Brazillein compound isolate	- Cytotoxic activity - Cell cycle analysis, induction of apoptosis and MMP9 activity	-	- IC50 50 ± 0,3 M on 4T1 cells - Mechanism of inhibition of MMP9 and Rac1 protein expression.
19.	Hanif et al., 2019	*Caesalpinia sappan L*. Ethanolic Extract Decrease Intracellular	*In vitro* using the MTT assay and *flowcytometry*	Ethanol extract	- Cytotoxic activity by MTT assay	Doxorobusin	- IC50 25 µg/mL on 4T1 cells

		ROS Level and Senescence of 4T1 Breast Cancer Cells			- Intracellular ROS expression analysis		- The mechanism does not go through the ROS pathway
20.	Hanif et al., 2017	The Effect of Sappan wood Extract (*Caesalpinia Sappan L.*) on the glutathione S-Transferase (GST) enzyme in 4T1 cancer cells	- *In vitro* using MTT assay and Flowcytometry - *in silico* use*molecular docking*	Ethanol extract	- Cytotoxic activity - Intracellular ROS expression analysis - GST activity	-	- IC50 22 µg/ml in 4T1 Breast Cancer Cells. - The mechanism is not through GST inhibition
21.	Khamsita et al., 2012	Ethanolic Extract of Sappan (Caesalpinia sappan L.) Wood Performs as Chemosensitizing Agent Through Apoptotic Induction on Breast Cancer MCF-7 Cells	*In vitro* using the MTT assay and*Flowcytometry*	Ethanol extract	- Cytotoxic activity by MTT assay - Analysis of apoptosis induction	Doxorobusin	- IC50 37 µg/ml on MCF-7 cells - provides a synergistic effect with the combination of doxorubicin through the induction of apoptosis.
22.	Jang et al., 2020	Roles of JNK/Nrf2 Pathway on Hemin-Induced Heme Oxygenase-1 Activation in MCF-7 Human Breast Cancer Cells	*In vitro* using the MTT assay and*western blot*	Brazilin compound isolate	- Cytotoxic activity - Hemin-Induced HO-1 Expression Activity - JNK activation analysis	-	The mechanism of hemin-induced inhibition of HO-1 expression is through inactivation of JNK/Nrf2 in MCF-7 cells.

23.	Lee et al., 2011	Mechanism of sappanchalcone-induced growth inhibition and apoptosis in human oral cancer cells	*In vitro* using the MTT assay and*Flowcytometry*	Sappanchalcone compound isolate	- Cytotoxic activity - Analysis of apoptosis induction	-	Mechanism of induction of apoptosis via p53, ERK, p38, JNK, and NF-KB signaling in human oral cancer cells
24.	Jenie et al, 2018	The Cytotoxic and Antimigratory Activity of Brazilin-Doxorubicin on MCF-7/HER2 Cells	*In vitro* using the MTT assay,*flow cytometry* Dan cytoSelect™	Brazilin compound isolate	- Cytotoxic activity - Analysis of apoptosis induction, cell cycle migration and invasion	-	- IC50 54 ± 3,7 M on MCF-7/HER2 cells - Mechanism of G2/M phase cell cycle inhibition, induction of apoptosis in the bcl-2 pathway, migration and invasion
25.	Harnis et al., 2020	Virtual Inhibition Analysis Of Bioactive Compound Brazilin (*Caesalpinia sappan L.*) Towards Progesteron Receptor or Lonaprisan in Breast Cancer Proliferation	*In silico* use*molecular docking*	Brazilin compound	Virtual analysis of ligand and receptor interactions	lonaprisan	The bond energy of the PR-Brazilin-Progesterone interaction is higher than that of the PR-LP (PR-Lonaprisan-Progesterone) interaction with a difference of 2.1kJ/mol.
26.	Utami et al., 2020	Co-treatment of Brazilein Enhances Cytotoxicity of Doxorubicin on WiDr Colorectal Cancer Cells Through Cell Cycle Arrest	*In vitro* using the MTT assay and*Flowcytometry*	Brazilein compound isolate	- Cytotoxic activity - Analysis of apoptosis induction and cell cycle	- Doxorubisin (IC50 2 M)	- IC50 130 M in WiDr cells in colon cancer. - Mechanism of cell cycle arrest in G2/M with doxorubicin
27.	Kim, *et al*., 2015	Brazilin Isolated from Caesalpinia sappan Suppresses Nuclear	- *In vitro* using Immunoblotting	Brazilin compound isolate	- Analysis of BAF inhibition	-	- Reducing the volume size of cancer cells in mice

		Envelope Reassembly by Inhibiting Barrier-to-Autointegration Factor Phosphorylations	- *live*		- Analysis of decreased volume of cancer cells		- Mechanism of Inhibition of BAF Phosphorylation.

1. Compounds - Compounds in Sappan wood that Have Anticancer Effects

Sappan wood is one of the plants that can be used as a treatment for various diseases. Based on a total of twenty-seven studies that met the inclusion criteria, it was found that the compounds contained in sappan wood had an anticancer effect, namely *brazilin, brazilein, sappanchalcone, 3-deoxysappanchalcone (3-DSC), caesalpiniaphenol G, dan caesalpiniaphenol H.*

a. Brazilin

Brazilin is a component of the main flavonoid compound in sappan wood which structurally belongs to the isoflavonoid group (Robinson, 1995). *Brazilin* has a cytotoxic effect on breast cancer in MCF-7 cells, 4T1 cells and T47D culture cells through several pathways, including by inhibiting hemin-induced expression of HO-1 through JNK/Nrf2 inactivation in MCF-7 cells (H. Y. Jang *et al*., 2020). Besides that*Brazil* can also inhibit migration and invasion of MCF-7/HER-2 cells (Jenie *et al.*, 2018). Research journal of Kim *et al.*, (2012) stated that the *Brazilin* compoundmay be a potential therapeutic intervention agent alone or in combination with other drugs for the treatment of plasma cell cancer in U266 cells. Meanwhile, in research of Lee *et al.*, (2013) stated that *Brazilin* able to inhibit the growth of gliobastoma or brain cancer in U87 cells by inhibiting cell proliferation. Brazillin can also inhibit the growth of blood cancer cells by showing a cytotoxic effect on human acute myeloid leukemia (KG1) cells and acute myeloid leukemia stem cells (KG1a) (Ngernnak, *et.al*, 2018) and has an effect on inhibiting lung cancer by inducing A549 cell death by targeting BAF (Kim *et al.*, 2014).

b. Brazilein

Brazilein is a major compound content in sappan wood which is known to be used as an anticancer, one of which is breast cancer, blood cancer, and colon cancer.*Brazilein* has cytotoxic activity in breast cancer in MCF-7 cells, T47D cells and 4T1 cells through several pathways, one of which is through inhibition of the HER2 protein in MCF-7/ HER2 cells (Rachmady *et al.*, 2017) and through downregulation of GSK-3b/b-catenin in MCF-7 cells (Tao, *et.al,*, 2013). *Brazilein* also reported to increase the cytotoxic effect on doxorubicin and cisplatin by inducing apoptosis in T47D cells (Tirtanirmala *et al.*, 2015 and Utomo *et al.*, 2018) and has a cytotoxic effect on breast cancer by inhibiting the proliferation and migration of 4T1 cancer cells (Handayani et al., 2016). Besides that, in research journal of Kim *et al.*, (2012) stated that the *brazilein* compound can be a promising anticancer candidate because it has a cytotoxic effect on human blood cancer (leukemia). Meanwhile, in research of Utami *et al.*, (2020) stated that*brazilein* has low cytotoxicity against WiDr cells in colon cancer, however,*brazilein* can increase the cytotoxic activity of doxorubicin by increasing cell cycle arrest in G2/M.

c. Sappanchalcone

Sappanchalcone is a phenolic compound of the flavonoid group.*Sappanchalcone* to be one of the promising phytochemicals for developing new anticancer drugs against oral cancer in humans. *Sappanchalcone* isolated from sappan wood can inhibit proliferation and induce apoptosis through mitochondria-dependent p53, ERK, p38, JNK, and NF-kB signaling in human oral cancer cells (Y. Lee *et al*., 2011).

d. Deoxysappanchalcone (3-DSC)

3-Deoxysappanchalcone (3-DSC) is a chalcone-based chemical extracted from sappan wood*(Caesalpinia sappan L.).* Content *3-deoxysappanchalcone* (3-DSC) in sappan wood has the potential to be used as a potential anticancer therapy for esophageal cancer in ESCC cells. 3-DSC can inhibit the occurrence of esophageal cancer by inducing ROS-mediated apoptosis and provoking G2/M phase arrest of the cell cycle, MMP dysfunction, multi-caspase activity through the JNK/p38 MAPK signaling pathway in ESCC cells (Kwak *et al*., 2021).

e. Caesalpiniaphenol G dan Caesalpiniaphenol H

Two phenolic compounds viz*caesalpiniaphenol G* (1) and*caesalpiniaphenol H* (2) which is isolated from sappan wood is known to be used as a cancer drug. Both of these compounds can inhibit the growth of blood cancer by inducing apoptosis in HL-60 cancer cells. It was also mentioned that these two compounds showed effective inhibition on Hela cells and on *caesalpiniaphenol H* compound showed significant inhibition against LLC (lung) cancer cells. However, both compounds showed very weak inhibition in breast cancer in MCF-7 cells (Hung *et al.,* 2013).

2. Sappan wood Activity as Anticancer in *In Silico*, *In Vitro* And *In Vivo Stuudy*

a. In Silico Studies

In Silico is a computation-based test used to analyze a chemical compound and the resulting interactions. Method*in silico* which is often used*molecular docking*. Based on table 3.1 *Brazil*in and *brazilein* compounds in sappan wood is known to have predictive anticancer activity by interacting with HER-2 receptors and Bcl-2 proteins and can bind to progesterone receptors. In research of Rachmady *et al.*, (2017) has been *in silico studies* use *molecular docking* from *Brazil*in and *brazilein* compounds as the main compound of the ethanolic extract of sappan wood against HER-2 (3PPO) protein as a target receptor. As for value *rerank score* from *Brazilein, Brazilin*, compounds and the native ligand on HER-2 is -77; -73; -120. These results indicate that brazilein and brazilin compounds have a higher affinity value than the native ligand

for HER-2, but these two compounds have amino acids that are specific to the native ligand so they can interact with the HER-2 protein.

Research of Utomo *et al.* (2018) also conducted a test*in silico* through *molecular docking Brazilin* and *brazilein* compound on breast cancer cells. The results are known to be good *brazilein* and *Brazilin have* value *rerank score* which is higher than the original ligand with a score *docking* from *Brazilein, Brazilin,* and *native ligan* on the consecutive Bcl-2 protein is -76.51; -74.34; -149,94. *Rerank score* this is used as the affinity parameter, where the lower the value *rerank score* then the affinity value obtained is getting stronger. Meanwhile, in research of Harnis *et al*., (2020) showed the result that lonaprisan has the most stable binding energy with the progesterone receptor with a value of -333.8kJ/mol when compared to *Brazilin*. However, the results of the interaction when docked together with progesterone showed that the binding energy of the PR-BP interaction (PR-*Brazilin*-Progesterone) is higher than the PR-LP interaction (PR-Lonaprisan-Progesterone) with a difference of 2.1kJ/mol, so it can be concluded*Brazil* has a higher ability than lonaprisan to inhibit breast cancer when combined with natural ligands.

b. In Vitro Studies

Basically *in vitro,* sappan wood*(Caesalpinia sappan L.)* has a cytotoxic effect on several cancer cells, namely breast cancer, blood cancer, plasma cell cancer, brain cancer, cervical cancer, lung cancer, esophageal cancer, oral cancer, and colon cancer. This has been proven in several studies on the cytotoxic activity of sappan wood as an anticancer based on the inhibitor concentration (IC50) value in table 3.1. The ethanol extract of sappan wood is known to have the strongest cytotoxic effect on breast cancer with an IC50 value of 13.1 µg/mL in 4T1 cells (Haryanti *et al*., 2018). In addition, MCF-7/HER2 cells can also provide a cytotoxic effect with an IC50 value of 25 µg/mL (Rachmady *et al.*, 2017) and in T47D cells with an IC50 value of 35 µg/ml (Nurzijah *et al.*, 2012).

The brazilin compound in sappan wood is also known to have cytotoxic activity in blood cancer with IC50 values of 5.45 ± 0.36 and 5.62 ± 0.43 µ.mol/L in K562 and K562/AO2 cells (Tao *et al.*, 2011). In addition, it was also reported that phenolic compounds of *Caesalpiniaphenol G* has cytotoxic activity with a value of 16.7+ 2.2 µg/mL in HL-60 blood cancer cells, but its cytotoxic activity is lower when compared to adryamycin (Hung *et al*., 2013). Sappan wood is also known to have anticancer activity in plasma cell cancer by inhibiting U266 cells (Kim *et*

al., 2012), brain cancer through inhibition of U87 cell proliferation (Lee *et al.*, 2013), and colon cancer against WiDr cells in combination with doxorubicin (Utami *et al.*, 2020).

Research of Hung, *et.al*, (2014) also reported that testing for cytotoxic activity on methanol extract of sappan wood had an IC50 value of 26.5 ± 3.2 µg/in Hela cells. This shows that the methanol extract of sappan wood has the potential to be used as an anticancer of the cervix. Meanwhile, in research of Hung *et al.*, (2013) stated that testing of the cytotoxic activity of the caesalpiniaphenol H compound also showed significant inhibition of lung cancer cells (LLC) with an IC50 value of 42.5 + 5.1µg/mL. In research of Kwak *et al.*, (2021) it is also known that the 3-deoxysappanchalcone compound isolated from sappan wood has activity against esophageal cancer with IC50 values of 19.8 µ.mol/L and 12.2 µ.mol/L respectively in KYSE 30 and KYSE cells 410. Additionally *sappanchalcone* compound on sappan wood in in vitro study is known to inhibit proliferation in human oral cancer cells (Lee *et al.*, 2011).

c. In Vivo Studies

In Vivo is study on living things such as mice, rats, rabbits, guinea pigs, pigs, dogs or primates. Through this test it will be possible to predict the effects of drug use in humans. Research of Kim's *et al.*, (2016) carried out a thorough test*live* using mice as animal experiments. This research was conducted with the aim to analyze cancer growth seen using *bioluminescence imaging* and measure the volume of cancer with caliper. In this study, each rat was injected subcutaneously with A549-FIG cells. When the size of the cancer reaches a diameter of 5 mm, then do administration of 20 and 40 mg/kg *Brazilin* in the treated rat group and 10% DMSO in the negative control group for 2 weeks. The results obtained were that the tumor volume increased in the control rats but decreased in the brazilin treated rats in a concentration-dependent manner.This shows that brazilin compound in sappan wood has an anticancer effect in in vivo studies.

3. Mechanism of Sappan wood as Anticancer

The mechanism of inhibition of sappan wood as an anticancer compound is known to be through several pathways, namely through induction of apoptosis, cell cycle inhibition, antimetastatic, antiproliferative, inhibition of HO-1 expression and inhibition through BAF. The following is a table of the mechanism of compounds in sappan wood as anticancer.

Table 2. Compound Mechanisms in Sappan wood as Anticancer

References	Compound	Type of cancer	Mechanism
Rachmady*et al.*, 2017	*Brazilein dan Brazil*	Breast cancer (MCF 7/HER2 cells)	Inhibits the HER2 protein.
Person*et al.*, 2011	*Brazilein*	Blood cancer (K562/AO2 leukemia cells)	Induction of apoptosis
Person*et al*, 2013	*Brazilein*	Breast cancer (MCF-7 cells)	Downregulation of CD1 protein and inhibition of the G1 cycle through the GSK-3b/b-catenin pathway
Kim *et al.*, 2012	*Brazilin*	Plasma cell cancer (multiple myeloma cell U266)	Inhibition of HDAC through induction of apoptosis and inhibition of the G2/M phase of the cell cycle
Lee *et al.*, 2013	*Brazilin*	Brain cancer (U87 cells)	Inducing apoptosis through the Caspases pathway.
Hung *et al.*, 2013	*Caesalpiniaphenol G*	Blood cancer (HL-60 cells)	Inducing apoptosis through caspase-3 activation.
Tirtanirmala*et al.*, 2015	*Brazilein*	Breast cancer (Cell culture T47D)	Induction of apoptosis
Utomo*et al.*, 2018	*Brazilein*	Breast cancer (Cell culture T47D)	Induces apoptosis. through the p53-independent pathway by targeting Bcl-2
to Ngern,*et al.*, 2018	-	Cancer cervix (cell HeLa)	Cell cycle inhibition by p53 stabilization.
(Haryanti et al., 2018)	*Brazilin dan brazilein*	Breast cancer (4T1 cells)	Inhibition of MMP-9 expression
Lee *et al.*, 2011	*Sappanchalcone*	human oral cancer	Inducing apoptosis via mitochondria by activation of ERK, p38, JNK, and NF-KB signaling

Kwak *et al.*, 2021	*3-deoxysappanchalcone*	esophageal cancer (ESCC cells)	Induces ROS-mediated apoptosis by activating p38 and JNK pathways, MMP dysfunction, multi-caspase activity and cell cycle arrest.
Handayani*et al.*, 2016	*Brazilein*	Breast cancer (4T1 cells)	G2/M phase cell cycle inhibition and inhibition of MMP9 and Rac1 protein expression.
Jang *et al.*, 2020	*Brazilin*	Breast cancer (MCF-7 cells)	Hemin-induced inhibition of HO-1 expression through JNK/Nrf2 inactivation.
Jenny*et al.*, 2018	*Brazilin*	breast cancer (MCF-7/HER2 cells)	Induction of apoptosis by suppressing Bcl-2 expression, inhibiting the G2/M phase of the cell cycle and inhibiting cell migration and invasion.
Harnis *et al.*, 2020	*Brazilin*	Breast cancer (progesterone receptor (PR)	Inhibits breast cancer through the Pogesterone pathway by inhibiting the binding of the native ligand to its receptor as an allosteric inhibitor.
Primary*et al.*, 2020	*Brazilein*	Colon cancer (WiDr cells)	enhances cell cycle arrest in G2/M
Kim *et al.*, 2015	*Brazilin*	Lung cancer (A549 cells)	Inhibits BAF Phosphorylation.

a. Apoptosis Induction Mechanism by sappan wood (Caesalpinia sappan) on Cancer Cells

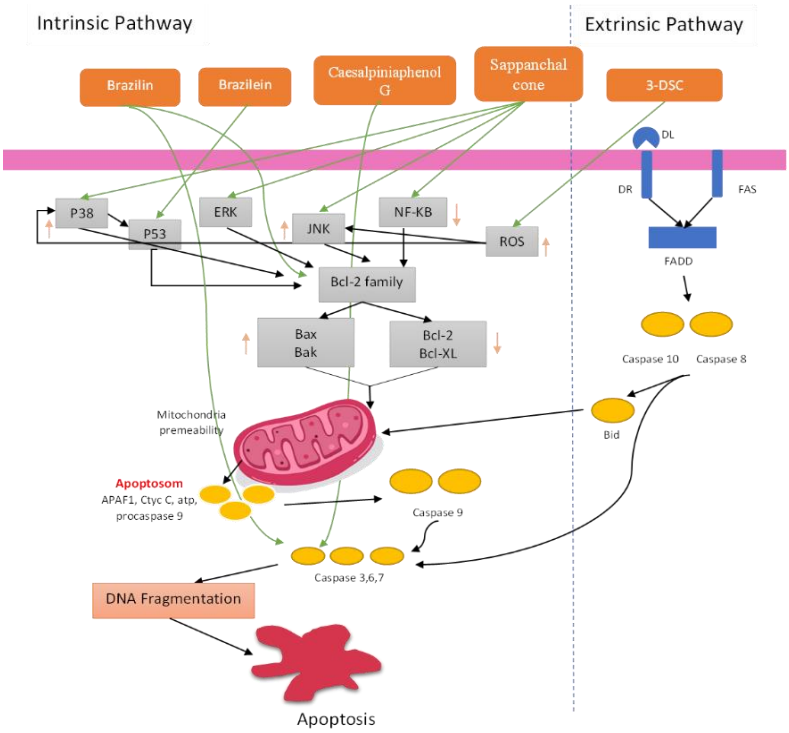

Figure 2. Mechanism of Apoptosis Induction by Sappan wood in Cancer Cells

One of the widely known anticancer effects of sappan wood is through the activation of the apoptotic pathway. The mechanism of induction of apoptosis can occur through two main pathways, namely the intrinsic pathway or the mitochondrial pathway and the extrinsic pathway or the death receptor pathway.*(Death Receptor*) (Purwaningsih, 2014). Based on table 2, the anticancer mechanism through the induction of apoptosis can be induced by several compounds from sappan wood, namely*brazilin, brazilein, Caesalpiniaphenol G, Sappanchalcone, dan 3-Deoxysappanchalcone* (3-DSC). The mechanism of induction of apoptosis induced by brazilin compounds occurs in plasma cell cancer, brain cancer, and breast cancer.*Brazilin* induces apoptosis through the mitochondrial (intrinsic) pathway and downregulates the anti-apoptotic Bcl-2 family proteins, such as Bcl-2 and Bcl-Xl (Kim *et al*., 2012). *Brazilin* can also induce apoptosis in U87 cells (brain cancer) through the caspase pathway. *Brazilin* activates cleavage of caspase-3, caspase-7. The activated caspase 3 will induce DNA fragmentation and cause apoptosis in U87 cells (Lee *et al*., 2013). In addition, the mechanism of induction of apoptosis can be induced by *brazilein* in blood cancer and breast cancer. In research (Utomo *et al.*, 2018)

brazilein can induce apoptosis in breast cancer cells (T47D culture cells) through the p53-independent pathway by inhibiting the Bcl-2 protein.

Sappanchalcone compounds also has mechanism of induction of apoptosis can occur in human oral cancer through the mitochondrial pathway by activating ERK, p38, JNK, and NF-KB. Activation of p38 causes phosphorylation of p53 which stimulates apoptosis (Lee *et al*., 2011). Meanwhile, decreasing NF-κB can inhibit apoptosis by reducing Bcl-2 transcription (Ratnasari*et al.*, 2016). Another sappan wood compound namely *caesalpiniaphenol G* also known to be able to inhibit the growth of blood cancer (HL-60 cancer cells) by inducing apoptosis through activation of caspase-3 (Hung *et al*., 2013). Meanwhile in *3-deoxysappanchalcone* (3-DSC) compounds is known to induce apoptosis in lung cancer. *3-deoxysappanchalcone* (3-DSC) Compounds causes increased ROS production in ESCC cells. Where an increase in ROS can induce apoptosis by activating the p38 and JNK pathways. In addition, increased levels of ROS are also able to downregulate mitochondrial function and multi-caspase activity (Kwak *et al.*, 2021).

b. Cell Cycle Inhibition Mechanism by sappan wood (*Caesalpinia sappan*) on Cancer Cells

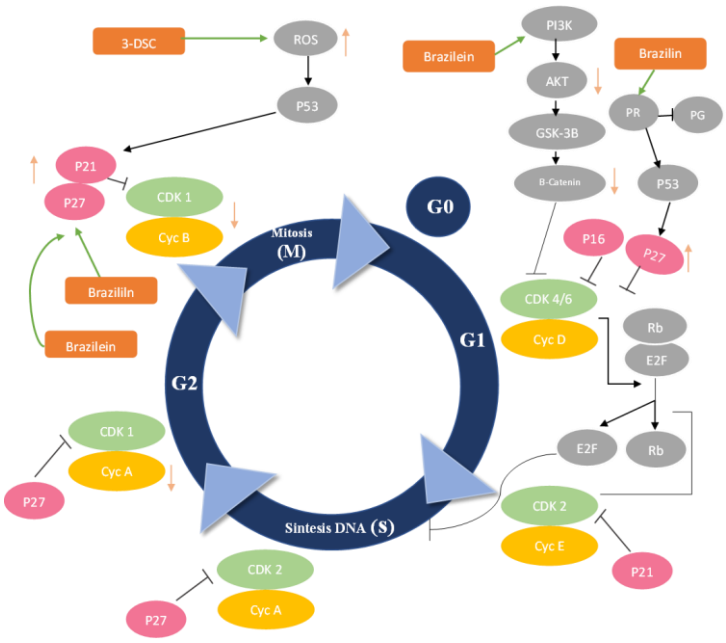

Figure 3. Mechanism of Cell Cycle Inhibition by Sappan wood on Cancer Cells

The cell cycle is a vital process in the life of every organism. Normally, the cell cycle results in cell division. In general, cell division is divided into 2 stages, namely mitosis (M), which is the

division of 1 cell into 2 cells, and interphase, which is the process between 2 mitoses. Interphase consists of phases G1 (pre-DNA synthesis), S (DNA synthesis), G2 (pre-cleavage) (Sarmoko, 2012). The mechanism through inhibition of the cell cycle can be induced by several compounds from sappan wood, namely brazilin, brazilein, and *3-Deoxysappanchalcone* (3-DSC). Mechanism of cell cycle inhibition by compounds*Brazil* occurs in plasma cell cancer and breast cancer. *Brazilin* can be used as an anticancer plasma cell by inhibiting the cell cycle in the G2/M phase. Significantly *Brazilin* attenuated the expression of cell cycle-related proteins such as cyclin D1, cyclin B1, and cyclin E, and also activated CDK inhibitors such as p21 and p27 in U266 cells (Kim *et al*., 2012). In breast cancer, *Brazil*in compound also performs an inhibitory mechanism in the cell cycle through the G2/M phase (Jenie *et al.*, 2018). *Brazilin* also known to inhibit breast cancer by inhibiting the binding of the original ligand (progesterone) to its receptor (progesterone receptor) so that it can cancel the activation of the progesterone receptor (Harnis *et al.*, 2020). The termination of the progesterone receptor causes an increase in p27 through activation of p53, this triggering the cell cycle arrest in the G1 phase (Azeez *et al*., 2015).

Other compounds in sappan wood namely *brazilein* can act as an anticancer breast by inhibiting the cell cycle in the G1 phase. Brazilein decreased the level of Akt and GSK-3b phosphorylation, followed by a reduction in b-catenin protein, thereby reducing the regulation of Cyclin D1 protein. This can trigger cell cycle arrest in the G1 phase (Tao *et al.*, 2013). Besides that *brazilein* can also inhibit colon cancer by inducing cell cycle arrest in the G2/M phase (Utami *et al*., 2020). Meanwhile in *3-deoxysappanchalcone* (3-DSC) compounds is known to be used as an anticancer in esophageal cancer. *3-deoxysappanchalcone* (3-DSC) is known to cause increased ROS production in ESCC cells. Increased ROS can cause the G2/M phase of the cell cycle to stop. 3-DSC increases the expression of p21 and p27 and inhibits the CDK/cyclin B1 complex, thereby triggering the G2/M phase termination in ESCC cells (Kwak *et al*., 2021).

c. Mechanism of Antimetastatic and Antiproliferative Cells by Sappan wood (*Caesalpinia*

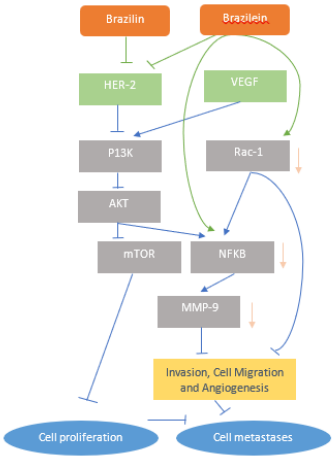

Figure 4. Mechanisms of Antimetastatic and Antiproliferative Cells by Sappan Wood on Cancer Cells

sappan) on Cancer Cells

Compounds in sappan wood, namely brazilein, are known to be used as anticancer agents in the breast by inhibiting proliferation, invasion and migration in 4T1 cancer cells by suppressing the expression of MMP9 and Rac1 proteins. *Brazilein* reported to decrease Rac-1 expression thereby significantly contributing to decreased cell migration. Besides that,*brazilein* also decreased MMP-9 expression so that it would contribute to the inhibition of cell metastasis. MMP9 is one of the gene products regulated by NFkB activation. *Brazilein* inhibiting the nuclear translocation of the NF-kB protein, thereby suppressing the NF-kB signaling pathway and suppressing MMP-9 expression in 4T1 breast cancer cells (Handayani *et al*., 2016). *Brazilein* and *Brazilin* also reported to have an antiproliferative effect on breast cancer through inhibition of HER-2 (Rachmady *et al.*, 2017).

d. The mechanism of inhibition of HO-1 expression by Sappan Wood (*Caesalpinia sappan*) on Cancer Cells

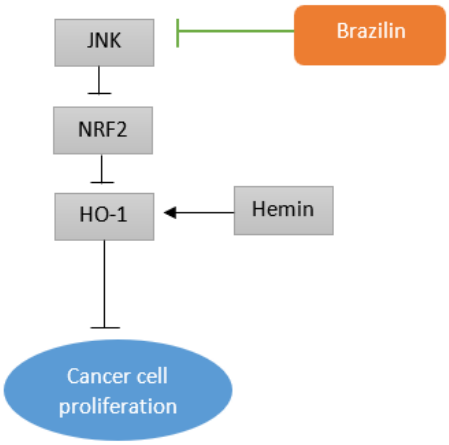

Figure 5. Mechanism of inhibiting HO-1 expression by Sappan wood in cancer cells *(*Jang *et al.*,2020).

Heme oxygenase-1 (HO-1) is a rate-limiting enzyme that is widely expressed in various disease conditions including cancer. Overexpression of HO1 in cancer cells can play a role in defense and induce cancer cell proliferation (Chau, 2015). Brazilin was reported to be able to inhibit hemin-induced expression of HO-1 through JNK/Nrf2 inactivation in MCF-7 cells. Hemin can induce HO-1 in cancer cells by increasing HO-1 expression. Hemin is known to only induce HO-1 expression through JNK/Nrf2 activation in MCF-7 cells. interestingly, *Brazilin* also only

significantly blocked JNK activation by hemin in MCF-7 cells. JNK activation is known to increase Nrf2 expression. Where the nuclear translocation of Nrf2 is an important mechanism in hemin-induced expression of HO-1 so that *Brazilin* also induces an inhibitory action on nuclear translocation of Nrf2. Hence, the clogging effect *Brazilin* on hemin-induced HO-1 expression in MCF-7 cells suggests useful therapeutic/preventive implications in breast cancer (Jang *et al.*, 2020).

e. BAF Inhibition Mechanism by Sappan wood (*Caesalpinia sappan L.*) on Cancer Cells

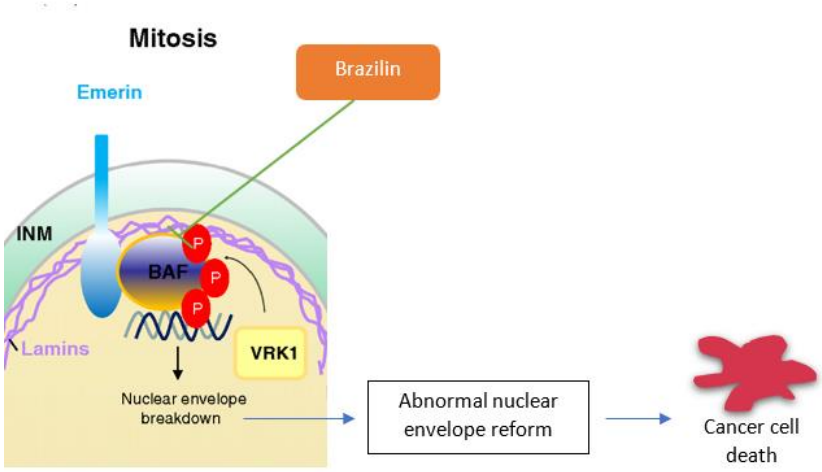

Figure 6. Mechanism of Inhibition of BAF by Sappan wood on Cancer Cells (Kim *et al*., 2015).

Protein *barrier-to-autointegration factor* (BAF) is a DNA-binding protein involved in assembling the nuclear envelope resulting in mitotic division. This nuclear protein is often over-expressed and plays an important role in the occurrence and development of cancer cells (Bailly & Vergoten, 2021). VKR1-mediated depletion or changes in BAF expression lead to changes in the nuclear envelope. Therefore, targeting inhibition of BAF phosphorylation can trigger synthetic death by destroying the nuclear envelope in cancer cells. one of the compounds known to inhibit BAF is *Brazilin*. *Brazilin* which was isolated from sappan wood was reported to be able to inhibit BAF phosphorylation so that it can block the reformation of the nuclear envelope during telophase. direct binding between *Brazil*in and BAF can inhibit the disruption of the relationship between DNA and the nuclear envelope. Inhibition of VKR1-mediated BAF phosphorylation induces abnormal reassembly of the nuclear envelope leading to cell death. This suggests that disruption of nuclear envelope assembly could be a new approach for anticancer therapy (Kim *et al*., 2015).

CONCLUSION

Based on the research results of the literature study conducted, it can be concluded, among others:

1. Compounds contained in the sappan wood plant (*Caesalpinia sappan L.*) which has anticancer activity, namely *brazilin, brazilein, sappanchalcone, 3-deoxysappanchalcone (3-DSC), caesalpiniaphenol G,* and *caesalpiniaphenol H.*
2. Sappan wood (*Caesalpinia sappan L.*) has predictive anticancer activity*in silico* on HER-2, BCl-2, and progesterone receptors. Sappan wood has anticancer activity in the test*in vitro* in breast cancer, blood cancer, plasma cell cancer, brain cancer, cervical cancer, lung cancer, esophageal cancer, oral cancer, and colon cancer based on the resulting cytotoxic activity. kindly*live*have anticancer activity by decreasing the volume of cancer induced in mice.
3. Compound on sappan wood *(Caesalpinia sappan L.)* has anticancer activity through several mechanisms, namely induction of apoptosis, inhibition of the cell cycle, antimetastasis and antiproliferative, inhibition of HO-1 expression, and inhibition of BAF

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