Pharmacological Activity of Mangrove Plant Bioactive Compounds Against Cancer Cell Changes: A Systematic Review

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Abstract. Cancer is a condition when the body's cells begin to grow abnormally and uncontrollably. Cancer therapy which is often used in medicine is non-selective, it can affect other normal cells that have a toxic effect in addition beside the activity as anticancer, to overcome this herbal plants have potential as anticancer one of them is mangroves. The research method uses a systematic review of the Science Direct, Pubmed, and Google Scholar databases that meet the inclusion and exclusion criteria. The results of the analysis show that the cytotoxic potential of cancer cells can be done by calculating the percentage of living cells with an IC50 value, which is a concentration that can kill half of cancer cells. The content of bioactive compounds from mangrove plant extracts include taurine, apigenin, lupeol, quercetin, alkaline benzoquinone, polyprenol and dolichol which have antioxidant and anticancer activity. These compounds work as mitogenic agents, namely inflammatory activation, cell mobility, angiogenesis, inhibition of protein kinases, antiproliferation, induction of apoptosis, and inhibition of metastasis.

Keywords: Mangrove · Bioactive Compound · Cancer Cells

1 Introduction

Cancer is a condition in which the body's cells begin to grow abnormally and uncontrollably. The rapid growth of this cancer is known as a malignant tumor. These cells attacks and destroy healthy tissue, including organs. Cancer sometimes starts in one part of the body and then spreads to other parts. This process is known as metastasis [1].

Cancer therapies is often used in cancer treatment are surgery, radiotherapy, chemotherapy, immunotherapy, but in practice therapies are considered to be still not effective even though they have shown therapeutic developments. This is because chemotherapy drugs are non-selective, meaning that chemotherapy drugs can affect other normal cells by giving toxic effects to these cells in addition to their anticancer activity, and to minimize these side effects, traditional plant medicines can be used or natural herbs that have potential as anticancer [2].

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Current cancer treatments are still not effective in healing, some are caused by the use of chemical drugs which are only temporary, now many anticancer drugs are developed from natural ingredients known as traditional medicinal ingredients. Anticancer is expected to have selective toxicity, meaning that it can destroy cancer cells without damaging normal tissue [3].

Mangrove plants have various types of bioactive compound from plant parts such as leaves, stems, bark, fruit and roots. The leaves contain compounds such as tannins, saponins, flavonoids, alkaloids, terpenoids, polysaccharides, steroids and phenolics. Bark and roots contains alkaloid compounds, terpenoids, flavonoids and phenolic compounds. In the twigs, pentacyclic triterpenoid compounds were found such as lupeol, oleanolic acid and betulinic acid. In mangrove fruit, phenolic compounds and based on the content of secondary metabolic compounds contained in mangrove plants, this plant has several bioactivities, including antioxidant, anti-inflammatory, antiviral, antibacterial, antimicrobial, cytotoxic activity, hypoglycemia, anticholesterol, antidiabetic., antimutagenic, antitumor and inhibit the proliferation of cancer cells [4].

Research by Darmadi et al., 2021 showed that the cytotoxic activity of the ethyl acetate extract of *Xylocarpus granatum* mangrove leaves was able to inhibit the growth of HT-29 colon cancer cells with an IC50 of 23,12 ppm. Another study regarding the cytotoxic activity of the methanol extract of mangrove leaves, *Phoenix paludosa* Roxb, was able to inhibit the growth of MCF-7 breast cancer cells with an IC50 of 36.71 g/mL. [2].

Based on the background that has been writed, the purpose of this study is to determine the cytotoxic effect of mangrove plants on cancer cells by systemic review.

2 Method

The method of this research is to search for articles using the Scient Direct, PubMed and Google Scholar databases with the keywords “cytotoxicity OR extract of mangrove OR cancer cell”. The types of articles analyzed used articles published in the last 10 years (2011–2021). In this research review, there are inclusion and exclusion criteria which are included in the inclusion criteria, namely mangrove leaf cytotoxic test, original research and cytotoxic activity in the form of IC50 value. Meanwhile, the exclusion criteria include articles that are not full text, have no IC50 value and are not original searches.

The article search results obtained from Science direct were 1 article, PubMed was 17 articles and Google Scholar was 14 articles. Articles were selected according to inclusion criteria by reading the title and abstract so as to obtain 0 articles that did not meet the inclusion criteria in Scient Direct, 9 articles on PubMed and 10 articles on Google Scholar. The results obtained after the selection by reading the titles and abstracts of articles that meet the inclusion criteria in Scient Direct are 1 article, PubMed 8 articles and Google Scholar 4 articles so that from 13 articles that meet the inclusion criteria and there is a theme of mangrove plant cytotoxic test and cytotoxic activity in the form of the IC50 value, then a review study is carried out (Fig. 1).

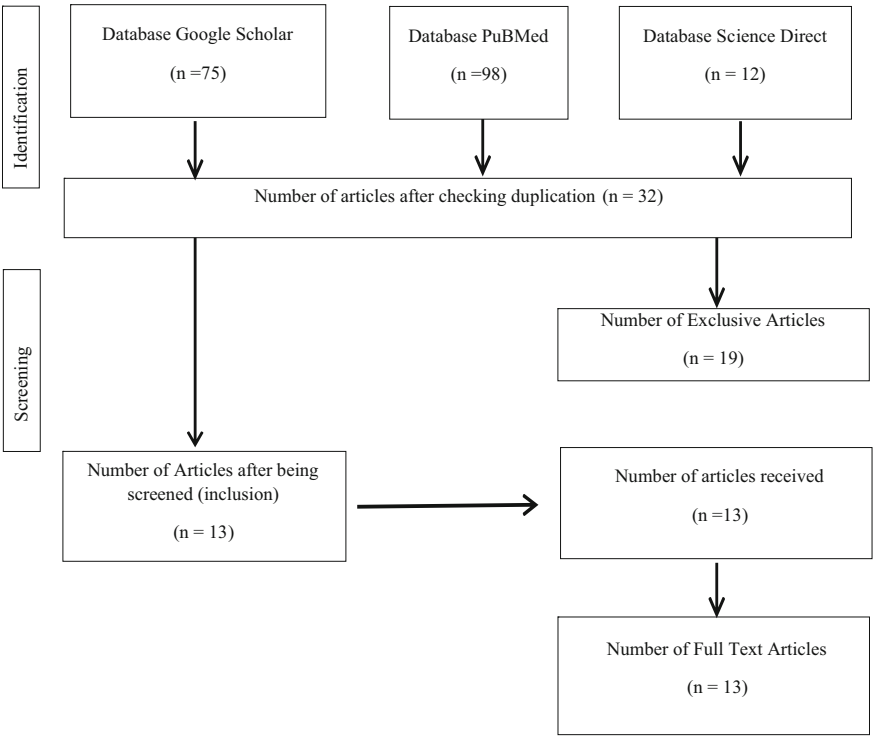


Fig. 1. Data Collection Strategy

3 Result and Discussion

The results of searching articles from the Scient Direct, PubMed and Google Scholar databases show that mangrove plants have potential as anticancer because it can be seen from the cytotoxic activity test of bioactive compounds.In this study, the results of the search for active compounds in mangrove plants were carried out on 8 species of mangrove plants, as presented in Table 1.

Based on the results of the search for articles as listed in Table 1, information regarding the cytotoxic activity of mangrove plants against cancer cells has been published internationally. The basic of the cytotoxic test is the ability of cells to survive in the presence of a given toxic compound. The ability of cells to survive can be defined as the absence of metabolic loss or proliferation and can be measured by increasing the number of cells, increasing the amount of protein, or DNA being synthesized. One of the cytotoxic tests is to measure the ability of cancer cells to survive in the presence of a given test compound [11]. The cytotoxic test was based on the resulting IC50 value parameter. Cytotoxic test was carried out by the MTT method. The principle of the MTT test is that the reductase enzyme reduces the yellow tetrazolium salt so that it turns into a tetrazolium succinate compound that enters the mitochondria to form purple formazan crystals and is insoluble in water. Furthermore, a stopper reagent which is detergenic is added to dissolve the purple crystal, measuring the color intensity (colorimetry) that

Table 1. Bioactive Compound on Mangrove Plants

Mangrove	Extract	Method	Secondary Metabolites	Bioactive Compound	Cancer Cell	IC 50 Value	References
Avicennia marine	Methanol Extract	Microtetrazolium (MTT)	Amino acid	Taurin	HeLa	321 µg/mL	Andriani *et al.*, 2021
Avicennia alba	Diethyl Ether Extract	Microtetrazolium (MTT)	Phenolic, alkaloids and terpenoids	Phenolic, alkaloids and terpenoids	MCF-7	25,1 µg/mL	Rahman *et al.*, 2017
Xylocarpus granatum	Ethyl Acetate Extract	Microtetrazolium (MTT)	Phenolic, alkaloids and flavonoids	Apigenin	HT-29	23,12 µg/mL	Darmadi *et al.*, 2021
Phoenix paludosa Roxb	Methanol Extract	Sulforhodamine B (SRB)	Triterpenoids	Lupeol	MCF 10A	36,71 µg/mL	Samarakoon *et al.*, 2016
Sonneratia paracaseolaris	Methanol Extract	Microtetrazolium (MTT)	Triterpenoids	Triterpenoids	Hella Cell	1,89 µg/mL	Gong *et al.*, 2017
Lumnitzera recemosa Willd	Petroleum Ether Fraction	Microtetrazolium (MTT)	Lignan, flavonoids	Quersetin	HL60	15,26 µg/mL	Thao *et al.*, 2015
Aegiceras corniculatum	Petroleum Ether Fraction	Microtetrazolium (MTT)	Quinone	1,4-benzaquinone	HL60	7,6–10,6 µg/mL	Li *et al.*, 2020
Avicennia alba Blume	Choloroform Extract and Methanol	Microtetrazolium (MTT)	Polyisoprenoids	Polyprenol and dolichol	WiDr	173.775 µg/mL	Illian, 2019

occurs as a result of the metabolism of a substrate by living cells into a colored product. This formazan crystal gives a purple color which can be read for its absorbance using an ELISA reader. Enzyme Linked Immuno Sorbent Assay (ELISA) is a measure of antigen or antibody in a sample [12].

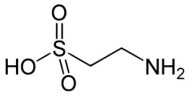
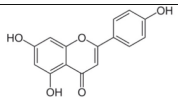
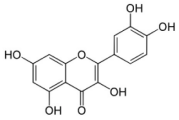
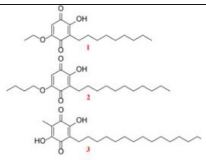
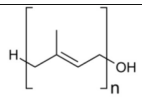
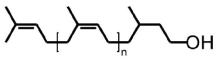
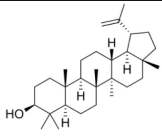
The IC50 value indicates the concentration that inhibits cell growth by 50% of the cell population, the smaller the IC50 value of the sample, the more toxic it is. Cytotoxicity has three levels according to the National Cancer Institute (NCI), those are very active if the IC50 value is <30 g/mL, moderately active with an IC50 value of 30–100 g/mL, and IC50 value >100 g/mL is declared inactive. The IC50 value <100 g/mL is still considered toxic and has antiproliferative properties (inhibits cell growth) even though the value is small. IC50 values below 100 g/mL indicate a potential as a chemoprevention agent, which means that the content of compounds in the extract can inhibit and suppress the process of carcinogenesis in humans so as to prevent the growth of cancer cells [11].

Observation of cytotoxic potential in cancer cells was carried out by calculating the percentage of living cells. The concentration of the sample was made into a log in order to obtain a more linear equation, then a linear regression equation was made between log concentration vs the percentage of living cells. The IC50 value is a concentration that can kill half of cancer cells [11].

Based on a literature review conducted by cytotoxic tests with several cancer cells including HeLa cells which are cervical cancer cells, HL60 cells are leukemia or blood cancer cells, MCF-7 and MCF 10A cells are breast cancer cells, HT-29 and WiDr cells are breast cancer cells. Colon cancer, and A549 cells are lung cancer cells. Almost all of them used the MTT Assay method to determine cytotoxic activity, but in Samarakoon et al., (2016) used the SRB Assay method. The SRB assay has been used since its development in the 1990s to perform various low-cost screening assays to test for cytotoxicity in cell-based studies. This method relies on the properties of SRB (sulforhodamine B), which binds to protein stoichiometrically under mild acidic conditions and can then be extracted under alkaline conditions so that the amount of bound dye can be used as a proxy for cell mass, which can then be extrapolated to measure cell proliferation [13]. In this study, identified the chemical structure of active compounds in mangrove plants as presented in Table 2.

Some of the content of bioactive compounds from mangrove plant extracts include taurine, apigenin, lupeol, forgetne, quercetin, alkaline benzoquinone, polyprenol and dolichol which have antioxidant and anticancer activity. Antioxidants are needed to prevent oxidative stress. Oxidative stress is a condition of an imbalance between the number of radicals present and the number of antioxidants in the body. Radicals are compounds that contain one or more unpaired electrons in their orbitals, so they are highly reactive and capable of oxidizing surrounding molecules (lipids, proteins, DNA, and carbohydrates). Antioxidants are very easily oxidized, so radicals will oxidize antioxidants and protect other molecules in cells from damage caused by oxidation by free radicals or reactive oxygen. Antioxidants also contribute to preventing radical attacks on cells. The imbalance in the formation of free radicals and their use in metabolism is called oxidative stress. The state of oxidative stress increases the opportunity for radicals to play a role in carcinogenesis and changes in the nature of tumor cells to become malignant. ROS and RNS have an impact in the form of genomic damage and genetic instability. These free

Table 2. Chemical structure of bioactive compounds

Bioactive Compound	Structure	Bioactivity	References
Taurin		Inhibit cell proliferation, through the mechanism of radical scavenging by taurine compounds will result in decreased production of ROS (Reactive Oxygen Species).	Andriani *et al.*, 2021
Apigenin		Contains several –OH groups that can increase the hydrophobic and hydrophilic sites of the bilayer, leading to the activation of membrane enzymes and receptors that synergize with anticancer action, and can weaken the mitochondria of colon cells HCT-15 which triggers programmed cell death by mitochondrial lysis	Rahman *et al.*, 2017
Quersetin		Through inhibition of abnormal activation of protein tyrosine kinase which is an inhibitor of the DNA topoisomerase enzyme.	Samarakoon *et al.*, 2016
Benzokuinone Alkali		Inhibitory effect on protein kinase activity in tumor cells which led to the inhibition of PKC, EGFR, and FAK. PKC is a protein that plays a role in tumor promotion and cell mitogenesis.	Gong *et al.*, 2017
Poliprenol		Improve fluidity and stability of biomembranes and may be useful in enhancing cell and tissue scaffold interactions.	Thao *et al.*, 2015
Dolichol		Improve fluidity and stability of biomembranes and may be useful in enhancing cell and tissue scaffold interactions.	Li *et al.*, 2020
Lupeol		Triterpenoid-mediated induction of reactive oxygen species (ROS) has now been characterized as an important proteasome-independent pathway for downregulation of specificity protein transcription factors.	Darmadi *et al.*, 2021

radical species are also mitogenic agents through stimulation of growth factor receptors and have a role in inflammatory activation, cell mobility, and angiogenesis in the tumor tissue microenvironment [14].

Taurine is an antioxidant compound that can inhibit cell proliferation, through the mechanism of radical scavenging by taurine compounds will result in decreased production of ROS (Reactive Oxygen Species). Decreased ROS production will result in NF-kB being inactivated while the expression of COX and iNOS enzymes is suppressed, so that inflammation can be suppressed [15].

Apigenin contains several –OH groups that can increase the hydrophobic and hydrophilic sites of the bilayer, leading to the activation of membrane enzymes and receptors that synergize with anticancer action, and can weaken the mitochondria of colon cells HCT-15 which triggers programmed cell death by mitochondrial lysis [5].

Quercetin has anticancer activity through inhibition of abnormal activation of protein tyrosine kinase which is an inhibitor of the DNA topoisomerase enzyme. Topoisomerase is an enzyme that functions to cut twisted DNA due to the opening of double strand DNA by the helicase enzyme, twisting and then reconnecting. The enzyme works at the time of extension of DNA replication. Quercetin has the ability to stimulate apoptosis of HL-60 leukemia cancer cells by stimulating the release of cytochrome c from mitochondria [16]. Quercetin compounds are able to inhibit the process of carcinogenesis during the initiation and propagation process. When initiating quercetin works by stabilizing or binding free radicals such as oxygen radicals, peroxides, and superoxide [12].

Lupeol bioactive compounds can inhibit breast cancer cell proliferation at certain doses, Lupeol compounds can cause apoptosis as well as cell cycle arrest of human osteosarcoma through the target of phosphatidylinositol 3-kinase/AKT/mammalian rapamycin pathway [17].

Polyprenols have potential pharmacological activity against cancer, dyslipidemia, influenza and viruses. They have been shown to improve fluidity and stability of biomembranes and may be useful in enhancing cell and tissue scaffold interactions. In addition, polyprenols have shown potential efficacy in the treatment of liver disease, and it was reported that the use of polyprenols can be used as a cancer prevention in hepatitis virus infection [18].

Quinone is one of the derivatives of phenolic compounds that exhibit biological and pharmacological activities such as antifungal, antimalarial, antibacterial, anticancer and antioxidant. Quinones are divided into 4 groups, namely benzoquinone, naphtoquinone, anthraquinone, and isoprenoid quinone. Polysoprenoid which includes polyprenol and dolichol is a derivative of isoprene which has cytotoxic activity on colon cancer cells [19].

The secondary metabolites that have the most role as anticancer are flavonoids and phenolic acids. The role of flavonoid compounds in anti-cancer is thought to be through protein kinase inhibition, anti-proliferation, induction of apoptosis, inhibition of metastasis and angiogenesis. Flavonoid compounds were investigated to exert an inhibitory effect on protein kinase activity in tumor cells which led to the inhibition of PKC, EGFR, and FAK. PKC is a protein that plays a role in tumor promotion and cell mitogenesis. On the other hand, EGFR is a protein kinase that has a function in stimulating the growth and development of tumor cells. The role of flavonoids in preventing FAK activity causes

actively dividing cells and tumor cells to avoid tumorigenesis activity and cell migration that can cause metastasis. Another ability of flavonoid compounds as anticancer is through the induction of apoptosis by inhibiting protein kinases and a number of other molecules such as EGF, TGF-α, and bFGF that have a role in suppressing cell apoptotic activity. Flavonoid compounds also play a role in the regulation of MMP proteins. MMP has a function in the depletion and degradation of the extracellular matrix which can have an impact on increasing the possibility of cancer cell metastasis [20]. Then there are phenol compounds that tend to be easily soluble in water because they bind to sugars as glycosides or are present in vacuole cells. Polyphenols have strong antioxidant properties and can prevent oxidative stress associated with cancer. The content of phenolic compounds can increase the inhibitory effect on cancer cells [21]. Furthermore, there is potential for terpenoid compounds, one of which is as an anticancer agent with the mechanism of blocking the cell cycle in the G2/M phase by stabilizing the spindle threads in the mitotic phase so that it can cause inhibition of the mitotic process. The next stage will occur cell proliferation and trigger apoptosis [22].

4 Conclusion

Based on the results of the discussion, it can be concluded that mangrove plant extracts have cytotoxic activity against cancer cells so that they can be developed as anticancer drugs. Bioactive compounds that have anticancer activity include taurine, apigenin, lupeol, quercetin, alkaline benzoquinone, polyprenol and dolichol. These compounds work as mitogenic agents, namely inflammatory activation, cell mobility, angiogenesis, inhibition of protein kinases, antiproliferation, induction of apoptosis, and inhibition of metastasis.

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