Identification Of Phytochemical Compounds Of Noni Leaf Extract (Morinda Citrifolia) And Its Activity In Increasing Leukemia Cell Apoptosis

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Abstract: Leukemia is a blood cancer characterized by overgrowth of abnormal white blood cells due to disruption of the apoptosis process, which is cell death that controls the number of cells in the body. This malignancy causes the accumulation of cancer cells that damage normal tissues and disrupt the immune system. One of the plants that can stimulate apoptosis and inhibit the development of blood cancer cells is noni leaves. Noni (*Morinda citrifolia*) leaves are known to contain antioxidant compounds such as flavonoids, phenols, and saponins that play a role in neutralizing DNA damage and supporting apoptosis mechanisms. This study aims to identify the phytochemical content of noni leaf extract and review its potential activity in increasing leukemia cell apoptosis. The extraction process was carried out by maceration method using ethanol solvent, then the extraction results were tested phytochemically to determine the content of active compounds such as alkaloids, flavonoids, tannins, saponins, and phenolics. The results of the phytochemical test showed that noni leaf extract was positive for flavonoids, saponins, and phenolics which are known to have antioxidant, cytotoxic, and apoptosis induction activities.

1 INTRODUCTION

Cancer is a major public health problem worldwide and the second leading cause of death in the United States. The death rate caused by cancer continues to increase every year from 2014 to the present. One type of cancer that grows rapidly is blood cancer (leukemia) (Zainuddin & La Maru, 2019). Leukemia is a malignancy of blood cells characterized by abnormal white blood cells in the bone marrow (Wolley et al., 2016). This cancer occurs due to abnormal proliferation of leukocyte cells because white blood cells (B lymphocyte cells) experience abnormalities so that they do not function properly. In addition, these cells also experience uncontrolled division. Leukemia is characterized by an increase in the number of white blood cells (leukocytes) in the blood circulation or spinal cord. Patients with leukemia show symptoms such as susceptibility to infections, anemia and bleeding. There are 2 levels of leukemia, namely acute leukemia and chronic leukemia (Yuni, 2015).

Acute leukemia is defined as a malignancy of blood cells originating from the bone marrow, characterized by proliferation of white blood cells, with manifestations of abnormal cells in the

peripheral blood. Leukocytes in the blood proliferate irregularly, uncontrollably and their function becomes abnormal. Due to the process, other functions of normal blood cells are also disrupted to cause leukemia symptoms. Acute leukemia in children accounts for 30%-40% of childhood malignancies, which can occur at any age, with the greatest incidence occurring at the age of 2-5 years with an average incidence of 4-4.5 cases/year/100,000 children under the age of 15 years.2,3 Several studies have reported that the proportion of male patients is greater than female, especially after the first age of life. The proportion becomes more dominant at the age of 6-15 years. In the overall age group, the ratio of males to females in LLA is 1.15. Acute leukemia type LLA (acute lymphoblastic leukemia) is present in ±90% of cases, the remaining 10% are acute myeloblastic leukemia (AML), and acute mono cytic leukemia (AMoL). While chronic lymphocytic leukemia as well as eosinophilic, basophilic, megakaryocyte, and erythroleukemia are very rare in children. It is said that the incidence rate in developing countries is approximately the same, ranging from 83% for LLA and the remaining 17% for AML (Widiaskara et al., 2016).

Chronic leukemia is a state of crisis characterized by an imbalance of physical, social, and psychological conditions resulting in patients often experiencing feelings of disorganization, anxiety, fear, and other emotions. There are three forms of emotional responses that may appear, namely rejection, anxiety, and depression (Amylia & Surjaningrum, 2014). Families of children diagnosed with blood cancer are faced with difficult circumstances, ranging from worry, burden of care, and uncertainty regarding the treatment that will be undertaken. Adequate emotional and psychosocial support is needed to help patients and families adapt to the conditions faced (Nasution, 2021).

One of the impacts of leukemia is a change in the physical appearance of the patient, which can have its own psychological impact. Many people with chronic diseases such as leukemia experience emotional problems in their lives. Patients often feel different, limited or isolated. This is due to one of the chemotherapy treatments that cause hair loss. Changes in physical appearance resulting from treatment have psychological implications for children who have undergone leukemia cancer treatment. In general, a weak body image is associated with academic, social and psychological problems, low self-esteem, and the emergence of depressive symptoms (Nasution, 2021).

Conventional treatments such as chemotherapy, radiotherapy, and bone marrow transplantation, efforts to develop alternative therapies based on natural materials are increasingly being made to reduce the side effects caused by the main therapy. Conventional therapy has indeed proven effective in suppressing the development of leukemia. However, it often causes serious side effects such as hair loss, nausea, decreased immune system, and damage to healthy tissue (Sung et al., 2021). Therefore, the search for new therapeutic agents that are safer and more selective against cancer cells has become the focus of research in the last decade (Kumar et al., 2017).

One approach that is widely researched is the utilization of medicinal plants that are rich in bioactive compounds. Medicinal plants contain secondary metabolites that can work as antioxidants

and anticancer by inducing apoptosis, inhibiting cell proliferation, and suppressing cancer spread (metastasis) (Newman & Cragg, 2020). These bioactive compounds have the potential to provide cytotoxic effects on cancer cells without significantly damaging normal cells. Thus, research on the phytochemistry of medicinal plants is very important to find effective and safe natural anticancer agent candidates (Winarti & Rahayu, 2017).

Noni leaf (Morinda citrifolia) is one of the herbal plants that has long been used in traditional medicine in various countries, including Indonesia. Almost all parts of this plant are useful, such as roots, fruit, seeds, and leaves. Noni leaves are known to contain various secondary metabolites such as flavonoids, alkaloids, saponins, tannins, and phenolics (Mulyati et al., 2020). These compounds play a role in important biological activities, including as antioxidants, anti-inflammatory, antibacterial, and anticancer (Potterat & Hamburger, 2007). The presence of antioxidant compounds in noni leaves is thought to be able to protect cells from oxidative stress while supporting apoptotic mechanisms in cancer cells (Ali et al., 2016).

Flavonoids and phenolics are the main groups of compounds in noni leaf extract that are reported to have cytotoxic effects on several types of cancer cells. The mechanism of action of flavonoids in inducing apoptosis is thought to be through activating the mitochondrial intrinsic pathway, increasing the expression of pro-apoptotic proteins (such as Bax), and suppressing the expression of anti-apoptotic proteins (such as Bcl-2) (Salehi et al., 2019). Meanwhile, saponins and alkaloids have the potential to suppress cancer cell growth through cell cycle inhibition and induction of extrinsic apoptosis pathways (Setiawan et al., 2018). The combination of these various active compounds makes noni leaves a potential candidate in supporting leukemia therapy. In addition to flavonoids and phenolics, other compounds in noni leaves such as saponins, alkaloids, tannins, and terpenoids are also reported to contribute to anticancer activity. Saponins play a role in inhibiting cancer cell growth through induction of extrinsic pathway apoptosis and inhibition of angiogenesis (Setiawan et al., 2018). Alkaloids work by inhibiting the cell cycle and increasing oxidative stress that triggers cell death (Arunachalam et al., 2014). Tannins have dual properties as antioxidants and pro-oxidants that can cause DNA damage to cancer cells, while terpenoids can suppress the expression of transcription factor NF-κB and activate caspase-3.

The combination of various bioactive compounds makes noni leaves a potential candidate in complementary therapy of leukemia. Further understanding of the mechanism of action of secondary metabolites of noni leaves is very important to support the development of phytopharmaceuticals based on natural ingredients as anticancer agents. Identification of phytochemical content in noni leaf extract is an important first step in uncovering its therapeutic potential.

Phytochemical tests can provide an overview of the class of secondary metabolites contained in the extract, while literature searches support the understanding of the molecular mechanism of these bioactive compounds. With the research on phytochemical identification and activity of noni leaf extract in increasing leukemia cell apoptosis, it is expected to provide a scientific basis for the development of alternative natural-based therapies

that are safer and more effective in the treatment of blood cancer (Zainuddin & La Maru, 2019).

2 METHOD

Tools and Materials

The tools used in this research are basin, sieve, blender, glass funnel, beaker glass, erlenmeyer, stirring rod, rotary evaporator, and analytical scales.

The materials used are noni leaves, 70% ethanol solvent, distilled water.

Maceration

This study used maceration method of noni (*Morinda citrifolia*) leaf extract starting with maceration method used in noni leaf extraction because of its efficiency in extracting active compounds. This process is carried out at low temperatures to maintain the stability of heat-sensitive bioactive compounds. In addition, maceration is a simple and economical method that allows the solvent to interact longer with the plant material, increasing the amount of dissolved compounds. The preparation of extracts using the maceration method was chosen because of its simplicity and is commonly used in herbal plant extract research, especially for compounds that are not heat resistant such as noni (Prasonto *et al.*, 2017).

Immersion of ethanol solution in noni leaves, because ethanol is a polar compound and is able to extract various bioactive compounds, such as flavonoids and polyphenols. In addition, ethanol is a safe and easy-to-use solvent, with high volatility that facilitates the evaporation process to obtain concentrated extracts (Prasonto *et al.*, 2017). Noni leaves and ethanol will be homogenized with a sonicator in a duration of 30 minutes and let stand for 24 hours. The results of the silence are evaporated and produce a thick noni leaf extract.

Phytochemical Test

Phytochemical test is divided into 7 consisting of tannin test, triperpenoid test, steroid test, phenolic test, alkaloid test, saponin test, flavonoid test

- **Tannin Test**

For the tannin test, as much as 0.5 grams of noni leaf extract was weighed and put into a test tube, then 2 mL of distilled water was added with a dropper pipette to the tube containing the extract.

- **Triterpenoid Test and Steroid Test**

For the triterpenoid test and steroid test, as much as 0.5 grams of noni leaf extract was also weighed and put into a test tube, then 0.5 mL of $CHCl_3$ and 0.5 mL of acetic acid were added, followed by the addition of 2 mL of concentrated H_2SO_4, then the results were observed.

- **Phenolic Test**

Phenolic test as much as 0.5 grams of noni leaf extract was weighed and put into an erlenmeyer, then added 10 mL of 70% ethanol. From the solution formed, 1 mL was taken and put into a test tube, then 2 drops of $FeCl_3$ solution (5%) were added.

- **Alkaloid Test**

Alkaloid test, as much as 0.5 grams of noni extract was also weighed and put into a test tube, added 0.5 mL of 1% HCl and 2 drops of Dragendorff solution.

- **Saponin Test**

Sapronin Test, weighed as much as 0.5 grams of noni leaf extract and then put it in a test tube, added

hot water until the extract is submerged and then cooled, after cold shake for 10 minutes and see the results obtained.

- **Flavonoid Test**

Flaphonoid Test, weighed 0.2 grams of noni leaf extract sample and then put into a test tube, added 5 ml of ethanol and then heated for 5 minutes, added a few drops of concentrated HCl, added 0.2 grams of magnesium and seen the results obtained.

Literature Review

Noni leaf (*Morinda citrifolia*) leaves are known to contain various phytochemical compounds such as flavonoids, alkaloids, saponins, tannins, and phenolics (Mulyati *et al*., 2020). These compounds play an important role in biological activities, including as antioxidants, antimicrobials, anti-inflammatories, and anticancer. Flavonoids are able to act as electron donors that neutralize free radicals, thus protecting cells from oxidative damage. In addition, flavonoids can also modulate gene expression related to cell cycle and apoptosis (Salehi *et al*., 2019). Phenolics and tannins are also reported to have the ability to inhibit cancer cell proliferation through protein binding mechanisms, inhibition of certain enzymes, and high antioxidant activity (Rahman *et al*., 2018). Meanwhile, alkaloids function to inhibit DNA and RNA synthesis in cancer cells, thus disrupting the cell's ability to proliferate (Kusmita *et al*., 2019). Saponins are known to damage cancer cell membranes, increase cell permeability, and trigger apoptosis. Combination of various metabolites

3 RESULT

Noni leaves are cleaned and dried in the sun or oven to avoid damage to the compounds they contain. After drying, then mashed until smooth using a blender and filtered to get noni leaf powder. Then, extraction was carried out by soaking 625 mL of ethanol into the noni leaf powder. Maceration is a technique used to take the desired compounds from a solution or solid by soaking the material to be extracted. This method is done by soaking the noni leaf powder to break the cell wall and membrane due to the pressure difference between inside and outside the cell, so that the secondary metabolites in the cytoplasm will be dissolved in organic solvents and the extraction of compounds will be perfect because the length of soaking can be regulated. The ethanol solvent that flows into the cell can cause the protoplasm to swell and the cell content material will dissolve according to its solubility (Yulianingtyas & Kusmartono, 2016).

Maceration is one of the simple extraction methods widely used in phytochemical research to obtain secondary metabolite compounds from medicinal plants. The basic principle of maceration is the immersion of simplisia powder in a solvent at room temperature, so that active compounds can diffuse from the plant cell matrix into the solvent (Handoyono, 2020). The advantages of the maceration method are that the procedure is easy to perform, does not require complex equipment, and is able to maintain the stability of bioactive compounds that are thermolabile because it is done without high heating. In addition, this method also allows the selection of solvents that are in accordance with the

polarity of the target compound, so that the extraction results become more optimal (Azwanida, 2015).

Table 1. Phytochemical Test Results of Noni Leaf

Phytochemical Test	Result	Conclusion
Tannins	Blackish brown	-
Triterpenoids	Blackish green	-
Steroids	Blackish green	-
Phenolics	Blackish green	+
Alkaloids	Blackish green	-
Saponins	There is froth	+
Flavonoids	Purple magenta	+

(Source: Personal Documentation, 2024)

Based on the table of phytochemical test results, the identified secondary metabolite compounds are phenolics, saponins, and flavonoids while the unidentified secondary metabolite compounds are tannins, terpenoids, steroids, and alkaloids. Tannin testing can be done by adding FeCl3 to noni leaf extract, if the color reaction test results occur blue or blackish green, it indicates the presence of tannins. Tannin compounds are polar due to the presence of OH groups, if the sample is added FeCl3 10% there will be a color change such as dark blue or blackish green which indicates the presence of tannin compounds. In addition, tannin compounds with FeCl3 will hydrolyze to form a blue-black color (Sulistyarini et al., 2020). The results of the tannin test with FeCl3 showed negative tannins, because they were blackish brown.

Triterpenoids are compounds that exist in a number of large plants. Terpenoids are derived from isoprene molecules CH2=C(CH3)-CH2-CH3 and its carbon skeleton is formed by C5 atoms. In testing terpenoids using anhydrous acetic acid and H2SO4, a purple or orange color is formed indicating the presence of triterpenoids. Steroids are lipid derivative compounds that are not hydrolyzed, and function as hormones. In testing steroids using anhydrous acetic acid and H2SO4, the formation of a blue or green color indicates the presence of steroids. The reaction that occurs between steroids and anhydrous acetic acid is the acetylation reaction of the -OH group on steroids. The results of terpenoid and steroid tests with CHCL3 + acetic acid + H2SO4 showed negative because it was blackish green.

Alkaloid testing a number of extracts were put into a test tube dripped with 1% and 2% HCl to draw alkaloids from the simplisia, alkaloids are alkaline so that with the addition of HCl a salt will form. Then heated to break the bond between alkaloids that are not in their salt form, cooled, and carried out a precipitation reaction using Dragendorff's reagent. Dragendorff reagent obtained positive results with the formation of orange to brownish red precipitate. This precipitate is formed because the nitrogen in the alkaloid forms a bond with the K+ ion from the reagent, producing a potassium-alkaloid complex (Muthmainnah, 2019). Alkaloid compounds are antifungal because these compounds work by disrupting the constituent components of peptidoglycan in fungal cells, causing the failure of the process of cell wall formation as a whole and will cause the cell to die (Sari et al., 2022). Alkaloid test

results with 1% and 2% HCl showed negative alkaloids, because they were blackish green.

Phenolic is a compound that has several hydroxyl groups (-OH) on its aromatic ring. The phenol test added FeCl3 1% and formed a blackish green color because FeCl3 reacts with the -OH group. The color complex formed is thought to be partially iron (III) hexaphenolate. FeCl3 + ions hybridize d2sp3 orbitals so that Fe3 + ions have 6 empty orbitals filled by electron pair donors, namely oxygen atoms in phenolic compounds that have free electron pairs (Alviani et al., 2022). Phenolic test results with FeCl3 showed positive phenolic because it is blackish green.

Saponin testing a number of extracts were put into a test tube to which hot water was added, cooled and then shaken for 10 minutes. The test results showed the presence of foam, indicating that the extract was positive for saponins. Saponins have been shown to have leukemia, paralysis, asthma, rheumatism and anti-inflammatory activities. Saponins are colloids that dissolve in water and foam after shaking, have a bitter taste. In addition, saponins also have hemolytic properties, which can destroy red blood cells (Muthmainnah, 2019).

Flavonoid testing 0.2 grams of noni leaf extract was put into a test tube dissolved with 1 mL of 70% ethanol and then magnesium was added, then concentrated HCl was added. The addition of magnesium and concentrated HCl to reduce the glycoside bond with flavonoids. Glycoside bonds with flavonoids in plants must be broken by reducing these bonds to get positive results because a magenta purple color is formed (Muthmainnah, 2019). Flavonoid test results with concentrated HCl + magnesium showed positive flavonoids because they were purple-black (Muthmainnah, 2019).

Noni leaf extract is proven to have high antioxidant activity. Research (Rohman et al., 2016) reported that the water fraction of the methanol extract of noni leaves has antioxidant activity with an IC_{50} value of 123.72 µg/mL, while the total phenolic content and total flavonoids are strongly related to the antioxidant activity (r^2 = 0.982 and 0.947). These results confirm that phenolic and flavonoid compounds play an important role in neutralizing free radicals that can trigger DNA damage and cancer development, including leukemia. Another study by (Murtini & Setyawan, 2023) also showed that noni leaf extract has very strong antioxidant activity, with IC_{50} of 49.09 µg/mL, close to the potential of noni fruit extract (IC_{50} = 22.95 µg/mL). This high antioxidant activity is the basis that noni leaf extract can help suppress oxidative stress that plays a role in leukemia pathogenesis.

In addition to flavonoids and phenolics, noni leaves also contain alkaloids and anthraquinone-derived compounds such as damnacanthal. This compound is reported to be able to inhibit tyrosine kinase p56lck in vitro, an enzyme that plays a role in the regulation of cell growth and differentiation (Haryoto & Firdaus, 2020). Inhibition of this kind of signaling pathway is very important, because many cases of leukemia are related to overactivation of protein kinases that trigger abnormal cell proliferation. This potential opens up opportunities for the development of natural ingredient-based phytopharmaceuticals that are safer than conventional chemotherapy.

Saponins identified in noni leaf extract have great potential as antileukemia agents because they

are able to induce apoptosis or leukemia cell death. This mechanism occurs through the death receptor (Fas) pathway and the mitochondrial pathway that triggers the release of cytochrome c and caspase activation, thus inhibiting leukemia cell proliferation. Some studies also show that saponins can suppress the expression of antiapoptotic proteins such as Bcl-2 and Bcl-xL, and can increase selective cytotoxic activity against cancer cells (Elekofehinti et al., 2021). These effects make saponins a promising natural therapeutic candidate, although further research is needed regarding bioavailability and safety of long-term use.

Thus, the presence of alkaloids and saponins in noni leaves shows great potential in suppressing the development of blood cancer cells. Based on these findings, it can be concluded that noni leaf extract through the content of flavonoids, phenolics, and alkaloids, and saponins has the potential to be used as a supporting therapy for leukemia. The mechanism that may be involved is the ability of antioxidants in reducing oxidative stress, as well as the ability of certain compounds and can inhibit cancer cell growth signaling pathways.

4 CONCLUSIONS

It can be concluded that the phytochemical test of noni leaf extract (*Morinda citrifolia*) shows that the ethanol extract of noni leaf contains bioactive compounds in the form of flavonoids, phenolics, and saponins, while the tannin, terpenoid, steroid, and alkaloid tests show negative results. These active compounds are known to have antioxidant, cytotoxic, and apoptosis induction activities, which have the potential to inhibit proliferation and trigger the death of cancer cells, especially leukemia cells. Maceration with ethanol solvent proved effective in extracting secondary metabolites without destroying the stability of the compounds. The results of the phytochemical test are supported by the literature that flavonoids can increase the expression of pro-apoptotic proteins, phenolics are able to inhibit cancer cell proliferation, while saponins play a role in triggering extrinsic apoptosis pathways. Thus, noni leaf extract has the potential to be developed as a natural complementary therapy candidate in the treatment of leukemia, although further in vitro and in vivo studies are still needed to prove the effectiveness and safety of its use.

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