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Therapeutic implication of *Pleurotus ostreatus* on microRNAs expression in acute myeloid leukemia: A systematic review

Bernaditha Michelle Lesmana [1], Aulia Rahmi Pawestri [2], Michelle Anisa Ujianto [3], Khonsaa Aadilah [3], Zahrah Firdaus [3], Felita Galih Perwita Sari [3], Edwin Widodo [4], Eviana Norahmawati [5], Sofy Permana [6] and Agustina Tri Endharti [2,*]

[1] *Departmen of Medical, Bachelor Program of Medical, Faculty of Mathematics and Natural Sciences, Universitas Brawijaya, Indonesia.*
[2] *Department of Parasitology, Faculty of Medicine, Universitas Brawijaya, Indonesia.*
[3] *Department of Biomedic, Master Program in Biomedical Sciences, Faculty of Medicine, Universitas Brawijaya, Indonesia.*
[4] *Department of Physiology, Faculty of Medicine, Universitas Brawijaya, Indonesia.*
[5] *Department of Pathology Anatomy, Faculty of Medicine, Universitas Brawijaya, Indonesia.*
[6] *Department of Biology, Faculty of Mathematics and Natural Sciences, Universitas Brawijaya, Indonesia.*

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Abstract

Until now, the modality of choice for patients with acute myeloid leukemia (AML) is chemotherapy. However, chemotherapy has resulted in severe side effects, especially for AML patients aged over 60 years. In addition, cases of multidrug resistance (MDR) have been reported. *Pleurotus ostreatus* or oyster mushroom has been widely known to possess anticancer effects. The effect might be elicited by its active ingredients. On the other hand, miRNA as a therapeutic target is thought to interact with the active compounds of *Pleurotus ostreatus*, thus making it a potential complementary treatment for AML. This review was conducted to determine the effect of the active ingredients in *Pleurotus ostreatus* through their mechanism of action on certain miRNAs. The review was conducted using 49 literatures that have passed the quality assessment using the CRAAP criteria and the JBI checklist. The literature search was carried out using 4 databases, including PubMed, Research Gate, ProQuest, and Science Direct. The systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. The results of the systematic review were synthesized in a narrative review without using statistical tests. In summary, at the molecular level, the active compounds in *Pleurotus ostreatus* can regulate several miRNAs that affect the proliferation and apoptosis of leukemia cells. In the future, it is necessary to carry out molecular and clinical analysis regarding the relationship between the active compounds of *Pleurotus ostreatus* and the expression of AML-related miRNAs.

Keywords: *Pleurotus ostreatus*; MiRNA; Acute Myeloid Leukemia; PRISMA

1. Introduction

Acute myeloid leukemia (AML) is a haematological malignancy with the 10th highest mortality rate and the 15th highest incidence of malignant tumors. In general, this disease affects a group of people aged 67 years and about 30% of patients are over 75 years old. Many experts are concerned about AML because the prognosis worsens with age and accounts for 40% of patient fatalities[1].

* Corresponding author: Agustina Tri Endharti

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Currently, AML treatment modalities include chemotherapy, targeted drugs, immunotherapy, and surgical procedures. Until now, multidrug resistance (MDR) has been found in several leukemia patients with various mechanisms. On the other hand, therapeutic agents commonly used in chemotherapy procedures were found to have developed resistance. Some patients have been shown to fail to achieve complete remission (CR) or experience a relapse after previously successfully responding to the treatment given [2].

Therapeutic agents work specifically by binding to certain targets. In the treatment of leukemia, microRNA (miRNA) is a new target that is thought to interact with drugs. MiRNA dysregulation has been shown to cause hematopoietic abnormalities and has been found in patients with solid tumors and leukemia. In addition, decreased miRNA expression causes AML cell proliferation to become uncontrolled [3]. To avoid having too many side effects and developing drug resistance, research has started to investigate AML treatments made from natural substances that target cancer cells selectively. *Pleurotus ostreatus*, known as oyster mushrooms, is one of the natural substances that needs to be researched. Oyster mushrooms can be utilized as a supplemental therapy for acute myeloid leukemia because they have a role as an anti-neoplastic agent, according to the findings of various studies [4].

The amount of β-glucan in *Pleurotus ostreatus* is relatively high. Through PCR verification, it has been demonstrated that β-glucan increase the expression of numerous miRNAs, including miRNA122 [5]. Through regulation of the polo-like kinase 1 (PLK-1) pathway, miRNA122 expression lowers the risk of AML. The interaction of the active components in *Pleurotus ostreatus* with miRNA as a solution for the treatment of acute myeloid leukemia was explored in this systematic review through observations of various research publications.

2. Material and methods

Systematic Literature Review (SLR) is the research methodology that was used. Without applying statistical testing, the SLR data were synthesized using a narrative review. With predetermined inclusion and exclusion criteria, secondary data—the results of prior studies—were used to compile the literature for the systematic literature review. The authors use inclusion and exclusion criteria to conduct data searches in order to maximize the selection of data. These standards are used to choose the data that will serve as the basis for study.

Inclusion criteria used in this study are

- Research articles of AML.
- Research articles with *Pleurotus ostreatus* intervention.
- The research design used is *in vivo* or *in vitro* experimental, observational studies, original articles, or review articles.
- Time of article publication between 2011-2022.
- The language used in the articles is English.
- Research articles indexed by Scopus, Web of Science, and SCImago Journal Rank (SJR).

The exclusion criteria are

- Full-text research articles that cannot be accessed (not open access).
- The results of the quality assessment using the JBI checklist are less than 6 and one of the CRAAP criteria is not met.

To conduct the research, preselected databases, including PubMed, Science Direct, and ResearchGate, are first searched for relevant keywords. Screening will next be conducted using previously established inclusion and exclusion criteria. The process of selecting articles that met the inclusion and non-exclusion criteria was based on the quality using the JBI checklist and the CRAAP test. Additionally, descriptive analysis and data extraction were done. After that, the previously acquired data was composed into a literature review. The identity and data of the articles that have been found are presented in tabular form containing the author's name, year of publication, location of publication, research design, characteristics of research subjects, and research results.

Data analysis was presented descriptively using the narrative review method. Narrative review aims to identify and summarize published research articles. With this method, researchers can discover new areas of study that have not been extensively reviewed before. The inclusion criteria and research questions used in collecting the articles were not specific, so the number of search results for articles was higher.

3. Results

3.1. Selection literature

This *literature review* was conducted to determine the effect of *Pleurotus ostreatus* extracton miRNA expression in AML. The literature search flow is divided into 4 stages as listed in Figure 1. All stages are carried out using 4 databases including PubMed, ResearchGate, ProQuest, and Science Direct. At stage 1, 39 literatures were found, stage 2 produced 44 literatures, stage 3 produced 74 literatures, and stage 4 produced 40 literatures. A total of 148 literatures were excluded because 146 of them were not available in full-text form and 2 others were withdrawn from publication (retracted). Quality assessment was also carried out on the 49 included literatures. As a result, all of the literatures met the criteria for the articles included, such as meeting at least half of the JBI and 4 CRAAP criteria. Of all the active components in *Pleurotus ostreatus*, there are 6 active compounds that have significant antileukemic effects, including ethanol, β-glucan, lectin, phenol, terpenoids, and unsaturated fatty acids. Articles eligible for inclusion in the systematic review consisted of 9 articles on ethanol, 5 articles on β-glucan, 9 articles on lectins, 11 articles on phenols, 9 articles on terpenoids, and 6 articles on unsaturated fatty acids. The results of data extraction are listed in table 1.

3.2. Results evaluation quality literature

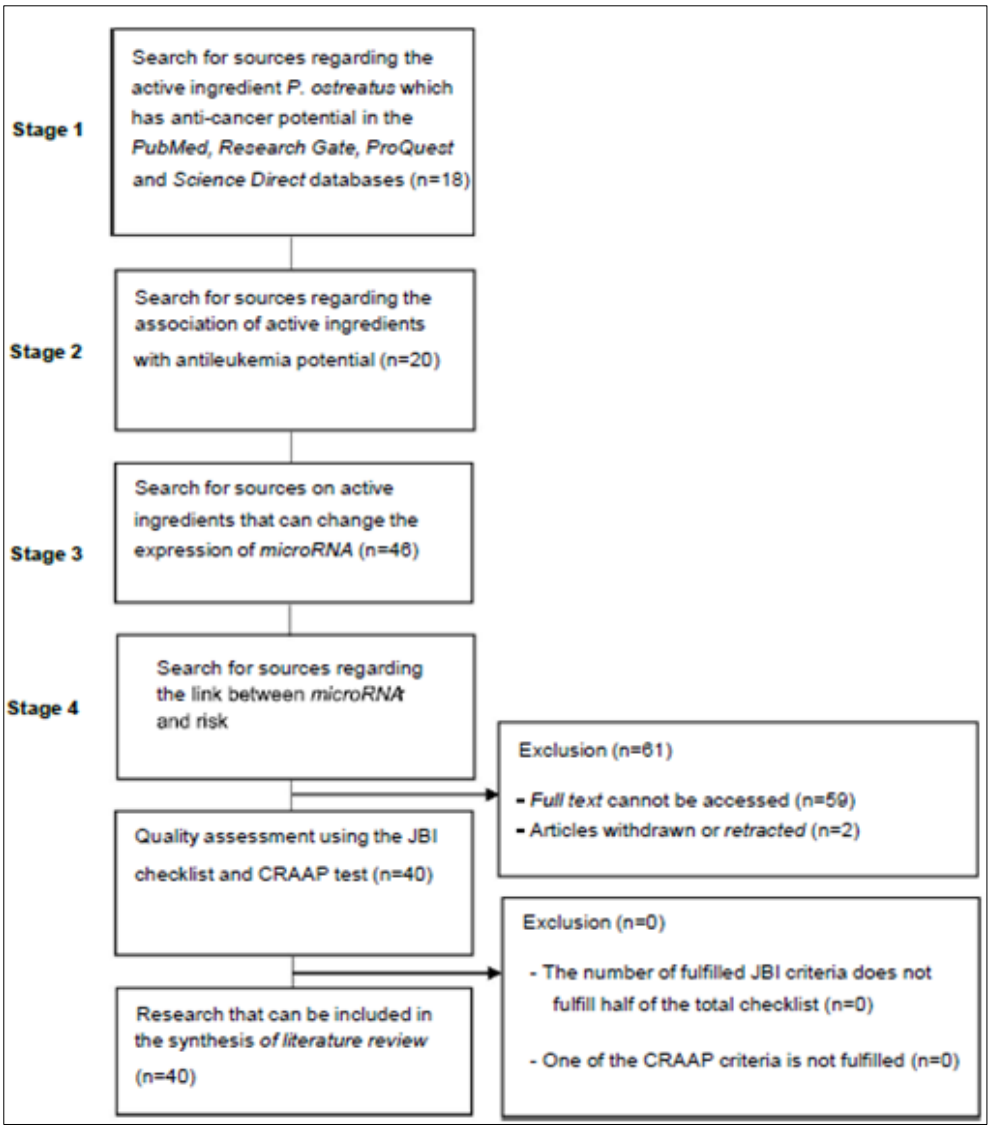

Figure 1 Flowchart of Literature Selection

Quality assessment was carried out using two instruments, including the CRAAP test and the JBI checklist. The CRAAP test is used for assessing the quality of the literature on various study designs by assessing the literature in general.

Meanwhile, the JBI checklist is more detailed because it can be adapted to the design of the studies being conducted, for example, experimental studies and systematic reviews.

In addition to the experimental study design, some of the literature used has a systematic review design. The review has a different structure from the experimental literature. Therefore, the checklist used is also different. The following is a JBI checklist for assessing the quality of literature with a systematic review study design:

The checklist was used to assess whether a literature matches the indicators provided. If literature to be used contained indicators in the CRAAP test and JBI checklist, it was noted as *yes* (Y). Conversely, if the literature did not have these indicators, it was written as *no* (N). If the literature was unclear regarding the indicator asked for, it was indicated as *unclear* (U). Literature was declared unfit for review if one of the CRAAP criteria or half of the JBI checklist was not met.

3.3. Analysis of critical appraisal

After conducting a quality assessment using the CRAAP criteria and the JBI checklist, 40 articles were concluded to be feasible for a systematic review. These articles contained active ingredients in *Pleurotus ostreatus* and its association with miRNA expression which had an effect on AML. Found article consisted of 5 articles on β-glucan, 9 articles on lectins, 11 articles on *phenolic acids,* 9 articles on terpenoids, and 6 articles on unsaturated fatty acids. After conducting a quality assessment of the articles, data extraction was carried out to describe the research components such as title, design, subject, and research results. The results of data extraction are presented in Table 1. In this stage, the data taken from the article was relevant data for the purpose of composing the systematic review carefully and accurately (Joanna Briggs Institute, 2020).

3.4. The active compounds of *Pleurotus ostreatus* which have potentially as anticancer in leukemia

Pleurotus ostreatus has an effect as an antileukemic agent used for complementary therapy of AML. Five of its active ingredients have the potential as antileukemic agents, such as β-glucan, lectin, phenolic acid, terpenoids, and unsaturated fatty acids [6, 7]. The six active ingredients above can regulate the expression of certain miRNAs that play a role in the pathway proliferation and apoptosis of cancer cells.

β-glucan is a carbohydrate consisting of glucose chains and soluble fibers found in many types of plants wheat. β-glucan obtained from *Pleurotus ostreatus* can reduce tumor volume and overall decreased the number of tumor nodules in mice induced breast cancer [6]. Research conducted by Jin *et al.* (2020) showed that β-1,3-D-Glucan (BFP) added to nano-sized selenium particles (BFP-Se) effectively inhibited proliferation and increased cytotoxicity against AML cells. BFP-Se treatment of U937 cells caused cells to swell and lyse [8].

Concanavalin A (Con A) is a type of lectin in the form of a matrix. Con A being one active ingredients contained in *Pleurotus ostreatus* besides β-glucan which has anticancer activity [6], a study conducted by Delebinski *et al*. *in vivo* against cell-injected NOD/SCID/IL2rg mice HL-60 proved that the lectin contained in the *Viscum album* (VAE) extract has the effect of increasing apoptosis. The pathways targeted by lectins are caspase 8 and 9 [9]. Supporting Delebinski's *et al.* (2015) results, a review conducted by Majeed *et al*. stated that lectins induce apoptosis in AML cells HL-60 by lowering the trans membrane potential (MTP) through the release of cytochrome C into the cytosol [10].

Pleurotus ostreatus as a fungus that is often used as a traditional medicine also contains active ingredients in the form of phenolic acid [7]. Phenolic acid in the form hispolon derived from *Phellinus igniarius* is effective both in suppressing cell proliferation and increasing cell apoptosis in AML. Nachliely *et al*. (2015) used carnosic acid conjugates, which is a form of polyphenolic acid with one of its derivatives vitamin D, such as the 1,25(OH)2D3 chain, as a treatment for AML cells [11]. The results prove that the conjugation can enhance the antileukemic effect against 3 types of leukemic cells, such as HL-60, U937, and MOLM-3 [11]. Therefore, in his review, Biersack (2016) stated that phenolic acid components such as curcumin, garcinol, flavonoids anthraquinones, xanthones, and anthracene derivatives may also be involved in affecting the expression of several miRNAs that play a role as a tumor suppressor or inducer of apoptosis, e.g. miRNA15a and miRNA16 [12].

Table 1 Summary of *in vitro* and *in vivo* studies of *Pleorotus ostreatus* and their phytochemicals evaluated for leukemia

Active ingredients	Researcher, Year, Country	Research design	Research Subjects	Research result
Poly-saccharide	Mishra, 2021, India	Systematic review	Patients with several types of cancer, including breast cancer, colorectal cancer, cervical cancer, hepatocellular carcinoma, and leukemia.	*Pleurotus ostreatus* contains active ingredients, such as β-glucan polysaccharides, ethanol, terpenoids, lectins, and unsaturated fatty acids, which can provide antineoplastic effects against leukemia.
	Ammoury, 2019, Lebanon	*in vitro*	Monomac-1 and KG-1 cell cultures.	*Annona cherimola* leaf extract, which is ethanolic, has an inhibitory effect on the proliferation of both cell cultures and does not have toxic effect on normal human mononuclear cells.
	McGill, 2014, United States of America	*In vitro* and *in vivo*	U937 and HL-60/VCR cells, C57BL/6J-Foxp3-RFP mice retroorbitally injected with C1498 cells.	*Oplopanax horridus* extract dissolved in ethanol reduced the viability of U937 and HL-60/VCR cells and increased the survival rate of rats by increasing the immune system response *in vivo*.
	Misir, 2020, Turkey	*in vitro*	MCF -7 breast cancer cells.	Turkish propolis extract which is ethanolic can increase cell arrest in the G1 cell cycle and also increase apoptosis in MCF-7 cells.
	Tseng, 2019, United States of America	Ex-vivo	Neural stem cells aspirated from dorsal telecephalic vesicles of male and female fetal rats (NSC).	Exposure to high doses of ethanol as much as 320 mg/dL, 70 mM, can increase the expression of miR-140-3p and miR-140-5p, thereby increasing the proportion of S cell cycle compared to G0/G1 cycle.
	Li, 2022, China	Ex-vivo	49 AML patients consisting of 30 male and 19 female patients; AML cells HL-60 and U937.	There was a decrease in miR-140 expression in AML patients and an increase in DNAJC3-AS1, so that the increased expression of miR-140 was followed by a decrease in DNAJC3-AS1. DNAJC3-AS1 plays role in inducing cancer cell proliferation and inhibits the role of miR-140 in suppressing cancer cell proliferation.
	Bassi, 2021, China	Ex-vivo	Bone marrow specimens taken from 60 AML patients.	miR-34 expression was decreased in AML patients, while circ-ATAD1 experienced an increase. circ-ATAD1 can decrease miR-34b expression and followed by increased AML cell proliferation.
	Peng, 2018, China	Ex vivo and *in vivo*	Bone marrow specimens of AML patients; KG-1a, THP-1, and KASUMI-1 cells obtained from AML-M2 patients injected into NOD/SCID or NOG mice.	MiR-34c-5p expression was lower in AML patients compared to normal hematopoietic cells. miR-34C-5p can induce senescence and inhibit AML cell proliferation. *In vivo*, increased miR-34c-5p expression in immunodeficient mice can lead to eradication of AML cells.
	Wang, 2015, China	Systematic review and	2597 cancer patients such as AML, glioma, lymphoma, pancreatic ductal adenocarcinoma, glioblastoma, NSCLC,	Increased expression of miR-34a is an indicator of good survival in cancer patients, especially cancer of the gastrointestinal system.

		meta-analysis	breast cancer, squamous cell carcinoma, Ewing sarcoma of bone, gastric cancer, adenocarcinoma of the esophagus, ovarian cancer, gastric mucosal lymphoid tissue lymphoma, and B-cell lymphoma.	
β-glucan	Mishra, 2021, India	Systematic review	Patients with several types of cancer, including breast cancer, colorectal cancer, cervical cancer, hepatocellular carcinoma, and leukemia.	*Pleurotus ostreatus* contains active ingredients such as β-glucan polysaccharides, ethanol, terpenoids, lectins, and unsaturated fatty acids which can provide antineoplastic effects against leukemia.
	Jin, 2020, China	*In vitro* and *in vivo*	AML cells THP-1, U937, HL-60, and Molm-12; 5-week-old female B-NSG mice injected intravenously with human AML cells mixed with G-CSF.	BFP-Se inhibits proliferation and increases toxicity in AML cells and *in vivo* antileukemic activity was found in mice which was characterized by slowed weight loss and increased survival rate.
	Zhang, 2019, China	*in vivo*	Sprague-Dawley rats (SD) were induced obesity by a high-fat diet.	Fermented barley plant extract can increase the expression of 10 miRNAs.
	Guan, 2020, China	*In vitro*, *in vivo* , and ex vivo	Human bone marrow stromal cells HS-5 and AML cells HL-60, THP-1, U-937, Kasumi-1; BALB/c mice injected with THP-1 and THP-1 transfected with ZEB2-AS1; bone marrow specimens of 36 AML patients.	ZEB2-AS1 activity is increased in AML patients. Reducing ZEB2 -AS1 activity can inhibit proliferation and increase apoptosis of AML cells by increasing miR-122-5p expression. miR-122-5p uses the PLK1 pathway as its target. A decrease in ZEB2-AS1 activity can inhibit the growth of tumor tissue in mice.
	Wang, 2018, China	Ex-vivo	AML patients aged over 14 years who have received induction chemotherapy.	TET1 expression is higher in AML patients with abnormal cytogenetics, which is accompanied by a worsening AML prognosis. Increased expression of oncogenes is associated with increased expression of miR-127-5p, miR-494, and decreased expression of miR-21, miR-616.
Lectins	Mishra, 2021, India	Systematic review	Patients with several types of cancer, including breast cancer, colorectal cancer, cervical cancer, hepatocellular carcinoma, and leukemia.	*Pleurotus ostreatus* contains active ingredients such as β-glucan polysaccharides, ethanol, terpenoids, lectins, and unsaturated fatty acids which can provide antineoplastic effects against leukemia.
	Delebinski, 2015, Germany	*In vitro*, *In vivo*, and ex vivo	U937 cells, HL-60 cells; NOD/SCID/IL2rg mice injected intravenously with 1x106 HL-60 cells; bone marrow aspiration of 2 pediatric AML patients.	Lectin and triterpenoids in the form of oleanolic acid can inhibit the proliferation of U937 and HL-60 cells. The combination of viscum extract containing lectin and triterpenoid extract containing I (viscumTT) can reduce the tumor mass of mice. Viscum extract can induce apoptosis of cancer cells through the loss of cell mitochondrial membrane potential.

	Majeed, 2021, India	Systematic review	Hepatocarcinoma, lung cancer, hepatoma, cervical cancer, leukemia, pancreatic cancer, and colon cancer.	Lectin has the effect of inducing apoptosis by releasing cytochrome C and proapoptotic factors and regulating the expression of genes involved in tumor cell growth, such as decreased expression of Bcl-2, metalloproteinase, c-Myc, Bax, Bad, and TNF.
	Bhutia, 2019, India	Systematic review	Cancer patients in general.	Lectin has anticancer and immunomodulating activity.
	Fu, 2012 , China	In silico	MCF-7 human breast carcinoma cells.	Lectins present in plants can block EGFR receptors which are involved in the binding between autophagic proteins and miRNAs.
	Shi, 2013 , China	In silico	Epidermal growth factor receptor (EGFR), HSP70, and HSP90 proteins.	Lectins present in plants can bind competitively to EGFR, TNFR1, HP70, and HSP90 which are regulated by several miRNAs.
	Zheng, 2020, China	Ex-vivo	Blood samples from 145 AML patients who did not undergo therapy prior to sampling.	miR-133 expression was decreased in AML patients compared to healthy patients. High levels of miR-133 in serum have a relatively high survival rate.
	Yamamoto, 2016, Japan	*in vitro*	AML HEL, K562, U937, HL-60, and THP-1 cells.	miR-133 has the effect of increasing sensitivity to chemotherapy.
Phenol	Cao, 2015, China	*In vitro* and *in vivo*	Human gastric cancer cells BGC-823; male BALB/c mice injected subcutaneously with 2x106 BGC-823 cells.	The content of other active ingredients such as phenol in *Pleurotus ostreatus* has an inhibitory effect on BGC-823 cells. *In vivo*, tumor weight and volume also decreased after treatment with *Pleurotus ostreatus*.
	Hsiao, 2013, Taiwan	*In vitro* and *in vivo*	AML3, MOLM-13, and MV4-11; NOD/SCID-IL2Rynull mice subcutaneously injected with 2x106 HL-60 cells.	Hispolon can suppress proliferation and also induce apoptosis of AML cells. *In vivo*, hispolon succeeded in reducing tumor growth in rats.
	Kim, 2014, Korea	*in vitro*	Jurkat AML, MM6, THP-1, and U-937 cells.	Obovatol can increase proapoptotic factor Bax, decrease antiapoptotic factor Bcl-2, and inhibit NF-kB activation.
	Nachliely, 2015, Israel	*in vitro*	AML cells HL-60, U937, and Molm-13.	Modification of 1,25(OH)2D2 can induce myeloid differentiation more strongly than 1,25(OH)2D3.
	Biersack, 2016, Germany	Systematic review	Cancer patients in general.	Active ingredients containing phenols and terpenoids can regulate the expression of miRNAs involved in cell proliferation and differentiation.
	Cione, 2020, Italy	Systematic review	Cancer patients in general.	Each nutritional supplement can influence the modulation of several different miRNAs.
	Liu, 2017, China	*in vitro*	Rheumatoid arthritis fibroblast-like synoviocyte (RA-FLS) cells.	Treatment using paeonol can reduce miR-155 expression.

	Testa, 2017, Italy	Systematic review	Patients with certain types of lymphoma and acute myeloid leukemia.	miR-155 utilizes the PI3K/AKT pathway as its target to increase cancer cell proliferation.
	Chan Li, 2019, China	*In vitro* and *in vivo*	HL-60 and SKM-1 human AML cells; male athymic mice inoculated with 1 × 10 HL-60 cells transfected with miR-21 mimic.	Increased expression of miR-21 can reduce the activity of Krüppel-like factor 5, so that AML cell proliferation increases. Overexpression of miR-21 results in increased tumor weight.
	Guang Li, 2018, China	*in vitro*	SKM-1, SH-SY5Y, SRA01/04 and Kasumi-1 cells.	Decreased miR-21 expression can inhibit SKM-1 cell proliferation, induce apoptosis, and cause cell arrest in the G1 phase.
	Vandewalle, 2020, Belgium	*In vitro* and ex vivo	AML K56 and OCI-AML3 cells; frozen bone marrow specimens of adult AML patients consisting of chemo-sensitive and chemo-resistant patients.	miR-21 decreased apoptosis induced by cytarabine and daunorubicin. miR-21 expression was increased in chemo-resistant AML patients.
terpenoids	Mishra, 2021, India	Systematic review	Patients with several types of cancer, including breast cancer, colorectal cancer, cervical cancer, hepatocellular carcinoma, and leukemia.	*Pleurotus ostreatus* contains active ingredients such as β-glucan polysaccharides, ethanol, terpenoids, lectins, and unsaturated fatty acids which can provide antineoplastic effects against leukemia.
	Meng Yang, 2018, China	*in vitro*	Human AML cells HL-60, THP-1, and U937.	Vibsanol A inhibits AML cell proliferation.
	Agents-Palmares, 2022, Spain	Systematic review	Patients with infection, cancer, and systemic inflammation.	Polyphenols and triterpenoids in *Olea europaea* can provide anti-carcinogenic effects.
	Tam, 2018, Vietnam	*in vitro*	OCI-AML human AML cells.	Monocyclic diterpenoids have the effect of reducing the number of OCI-AML cells.
	Chan Li, 2019, China	*In vitro* and *in vivo*	HL-60 and SKM-1 human AML cells; male athymic mice inoculated with 1 × 10 HL-60 cells transfected with miR-21 mimic.	Increased expression of miR-21 can reduce the activity of Krüppel-like factor 5, so that AML cell proliferation increases. Overexpression of miR-21 results in increased tumour weight.
	Guang Li, 2018, China	*in vitro*	SKM-1, SH-SY5Y, SRA01/04, and Kasumi-1 cells.	Decreased miR-21 expression can inhibit SKM-1 cell proliferation, induce apoptosis, and cause cell arrest in the G1 phase.
	Vandewalle, 2020, Belgium	*In vitro* and ex vivo	AML K56 and OCI-AML3 cells ; s frozen bone marrow specimens of adult AML patients consisting of chemo-sensitive and chemo-resistant patients.	miR-21 decreased apoptosis induced by cytarabine and daunorubicin. miR-21 expression was increased in chemo-resistant AML patients.
	Yang, 2022, China	*In vitro* and ex vivo	Kasumi-6 AML cells and HS-5 human bone marrow stromal cells; bone marrow specimens of AML patients who have received HHT-based chemotherapy.	M1R17HG expression has decreased in AML patients. miR-21 has the opposite effect to M1R17HG and PTEN in terms of HHT-induced apoptosis, where miR-21 increases resistance to chemotherapy.

	Zhang, 2021, China	*in vitro*	Human bone marrow stromal cells HS-5 and human AML cells HL-60, NB4, and Thp-1.	miR-21 expression is increased in AML patients. miR-21 suppresses the activity of the BCL11B pathway causing genetic mutations and the formation of oncogenes in AML patients.
Unsaturated fatty acids	Mishra, 2021, India	Systematic review	Patients with several types of cancer include breast cancer, colorectal cancer, cervical cancer, hepatocellular carcinoma, and leukemia.	*Pleurotus ostreatus* contains active ingredients such as β-glucan polysaccharides, ethanol, terpenoids, lectins, and unsaturated fatty acids which can provide antineoplastic effects against leukemia.
	Baroud, 2021, France	*in vitro*	HL-60 human AML cells.	The cytotoxicity of azacitidine conjugated with EPA and DHA is lower than that of azacitidine alone. The formulation also produces a low IC50.
	Nabavi, 2015, Iran	Systematic review	Patients with several types of cancer such as cachexia, breast, colorectal, gastric, pancreatic, esophageal, prostate, lung, head-neck, and leukemic cancers.	Omega-3 can reduce the proliferation and/or increase the apoptosis of leukemia cancer cells by modulating the transduction and expression of genes involved in the pathogenesis of leukemia and reducing systemic inflammation.
	Fussbroich, 2020, Germany	*in vivo*	Female C57BL/6 mice aged 6-8 weeks sensitized with house dust mite extract (HDM) to induce allergic asthma.	The combination of LCPUFAs managed to restore 21 of the 62 dysregulated miRNAs, of which 8 miRNAs were mmu-miR-146a-5p, -30a-3p, -139-5p, -669p-5p, -145a-5p, -669a-5p, - 342-3p and -15b-5p can return to normal levels.
	Nowicki, 2021, Poland	Ex-vivo	Blood samples from multiple myeloma patients, non-Hodgkin lymphoma patients, and Hodgkin lymphoma patients.	Patients with low levels of miR-146a-5p have high CD34+ cells. This has a good influence on the mobilization of stem cells given during chemotherapy
	Testa, 2017, Italy	Systematic review	Patients with certain types of lymphoma and AML.	miR-155 utilizes the PI3K/AKT pathway as its target to increase cancer cell proliferation.

AELE= Annona cherimela ethanolic leaf extract, MNC= Mononuclear normal cell, AML= Acute myeloid leukemia, EEP= Ethanolic extract propolis, NSC= Neural stem cell, BMMNCS= Bone marrow mononuclear cells, RT qPCR= Real time quantitative polymerase chain reaction, hCB= Human cord blood, BFP-Se= β-(1,3)-D-glucan-Selenium, LFBE= Lactobacillus plantarum dy-1, TT= Triterpenoid, POL= Polygonatum odoratum lectin, CML= Chronic myeloid leukemia, DMSO= Dimethyl sulfoxide, hADSC= Human adipose derived stem cells, KLF5= Krüppel-like factor 5, HHT= Homoharringtonine, EPA= Eicosapentaenoic acid, DHA= Docosahexaenoic acid, LCPUFA= Long chain polyunsaturated fatty acid, cLA= Conjugated linoleic acid, hucMSC= Human umbilical cord mesenchymal stem cell

Terpenoids are one of the most frequently used active ingredients found in mushrooms commonly consumed by humans (edible mushroom) such as *Pleurotus ostreatus.* With triterpenoid treatment, MCF-7 cells exhibited high antitumor activity with an IC50 of 15.71 μM [6]. Triterpenoids found in *Olea europea,* such as maslinic acid (MA), can activate the JNK pathway and p53 so that the expression of pro-apoptotic proteins, such as Bax and Bid, are also increased. Apoptotic pathway in the mitochondria cause activation of caspase pathways 3, 8, and 7 [13]. Terpenoids in the form of vibsanol A successfully inhibited the proliferation of AML cells, such as HL-60, U937, and THP-1. In addition, vibsanol A also induces cell differentiation that appear from the evaluation of cell morphological maturity, such as smaller nucleus-to-cytoplasmic ratio and larger nuclear distortion. PKC pathway activation targets vibsanol A, thereby increasing cell differentiation. MEK/ERK/MAP pathways are also activated after vibsanol A treatment on AML cells [14].

Linoleic acid is a form of polyunsaturated fatty acids that have effects as antitumor, immune modulation, and antioxidants [6]. The results of the review conducted by Nabavi *et al.* also stated that DHA is effective as a therapy against AML KG1a cells. The mechanism is by increasing DNA fragmentation via the Bax pro-apoptotic pathway. EPA and DHA treatment against U937 AML cells gave results in the form of increased expression of C/EBPÿ, which is a tumor suppressor gene. In addition, EPA can also increase apoptosis and necrosis in HL-60 cells [15].

3.5. Types of miRNAs that can be the target of AML therapy

Administration of LCPUFA to A549 cancer cells can increase the expression of hsa-miRNA146a-5p toward normal levels [16]. hsa-miRNA146a-5p is known to act as a tumor suppressor, so that the decreased expression will increase proliferation and decrease sensitivity to chemotherapy administered to leukemic cells. Additionally, the CXCL12/CXCR4 pathway is also a target for miRNA146a-5p. This pathway plays a role in reducing stem cell migration hematopoietic *(hematopoietic stem* cell/HSC).

Tang *et al.* (2021) performed *in vivo* research using β-glucan as the 9 miRNA treatment to evaluate changes in the miRNA expression. β-glucan can increase expression miRNA122 in infection-induced channel catfish bacteria [5]. Increase in miRNA122 expression *in vitro* using HL-60 cells and THP-1 inversely reduces polo-like kinase (PLK)-1 kinase [17]. PLK-1 is an important regulator of the cell cycle. miRNA122 suppresses PLK1 pathway activity, which can play a role in lowering excessive cell cycles [18].

The review conducted by Cione *et al.* (2021) mentioned that phenolic acid in the form of resveratrol can regulate miRNA expression, that is, decreasing the expression miRNA21 [19]. Resveratrol is a component of phenolic acid which is normally found in plants in isomeric forms of trans and cis [20]. Apart from phenolic acids, terpenoids in the form of ursolic acid can also decrease miRNA21 expression. miRNA21 increased resistance to chemotherapy agents against AML, such as cytarabine and daunorubicin. Vandewalle *et al.* (2021) in his research improves miRNA21 expression in K562 and OCI-AML3 cells using a lentivirus construct containing miRNA21. The results showed that the apoptosis induced by cytarabine and daunorubicin was decreased due to overexpression of miRNA21 [21]. Elevated miRNA21 expression in AML patients can induce AML cell proliferation by inhibiting BCL11B. BCL11B plays an important role in lowering expression of HDM2 or MDM2, which are oncogenes inducer of tumor formation, by inactivating the p53 pathway [22]. miRNA21 also degrades PDCD4 and ARL2 in K562 cells treated with cytarabine and daunorubicin [21]. PDCD4 and ARL2 are tumor suppressor pathways that often experience a decrease, even inactivation, in leukemia patients [23]. Inhibition of miRNA21 expression can also activate the PTEN/AKT pathway to modulate cancer cell proliferation and KLF5 play a role as a tumor suppressor in AML patients [24, 25].

Phenolic acid in the form of paeonol used by Liu *et al.* (2017) as a treatment for synovial *fibroblast-like* (FLS) for 24 hours can inhibit miRNA155 expression [26]. In addition, decreased expression of miRNA155 is associated with the inhibitory effect of FLS proliferation through activation of the FOXO3 pathway. FOXO3 is a transcription factor that plays role as a tumor suppressor [26]. miRNA155 acts as an oncogene in AML patients. The FLT3 signal cascade activated induce miRNA155 expression. Then, miRNA155 targets the PI3K/Akt enzyme SHIP1 phosphatase to activate the PI3K/Akt pathway. This, in turn, increases metabolism, proliferation, growth, and cell survival by involving phosphoinositide-3-kinase (PI3K) [3].

Lectins derived from plants have become widely used research materials because of their antitumor effects through the decreased expression of glycoconjugate receptors on the cell surface cancer, one of which is the epidermal growth factor receptor (EGFR) [27]. EGFR is abnormally activated in AML patients and becomes an inducer of tumorigenesis [28]. Decreased expression of these receptors can occur as a result of the miRNA presence that regulate EGFR receptors, i.e.. miRNA133. In AML patients, miRNA133 expression is impaired and the patient's prognosis worsens. Lectins may increase miRNA133 expression to reduce EGFR activity [29, 30]. In addition, miRNA133 acts on ectopic virus integration

site 1 (Evi 1) by the decreasing receptor activity. Yamamoto *et al.* (2016) mentioned that overexpression of Evi 1 is associatedwith the worsening prognosis of AML patients [31].

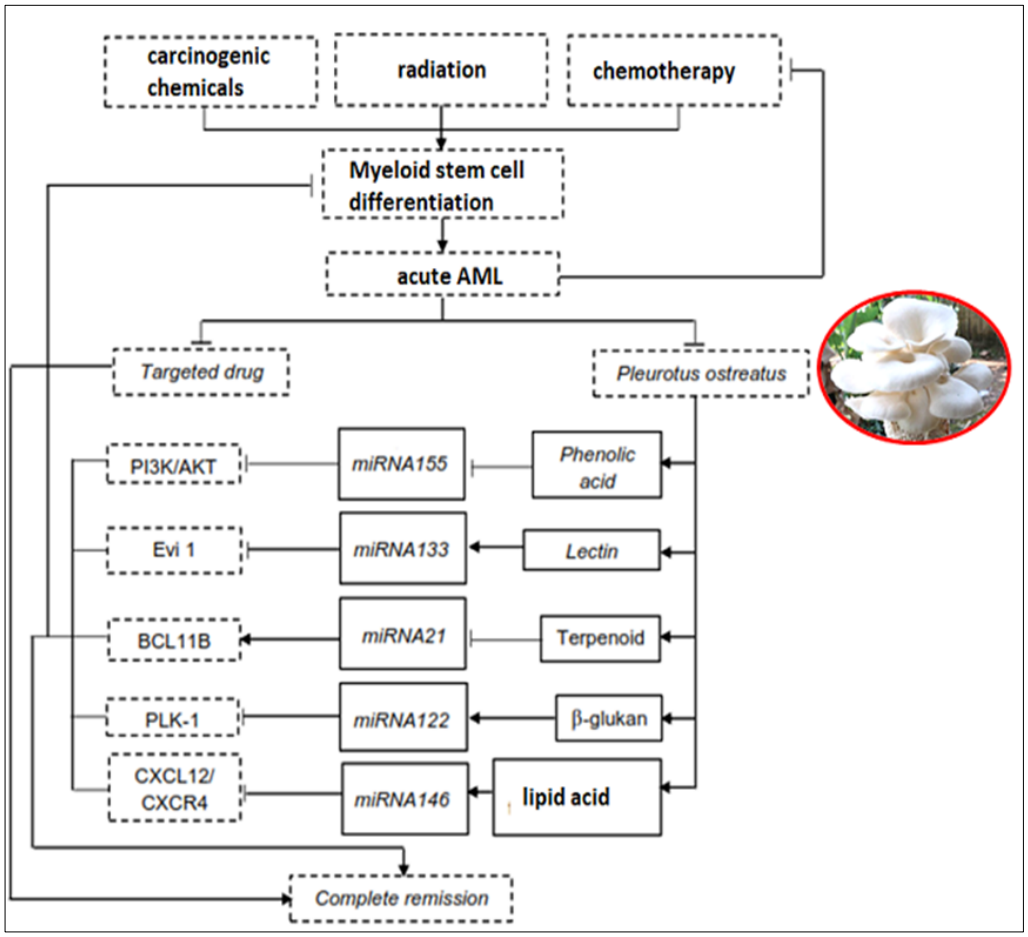

Figure 2 Anti-cancer activity of *Pleurotus ostreatus* and their mechanisms of action

4. Discussion

AML occurs when the differentiation of myeloid stem cells stops so that there is an accumulation of blast cells in the bone marrow and even reduces other normal cells in the peripheral blood circulation. In the pathogenesis of AML, genetic elements are involved, one of which is miRNA. miRNA expression can have different effects on AML cell proliferation and apoptosis, both inducing and inhibiting these processes [32].

Pleurotus ostreatus or more commonly known as oyster mushrooms have long been known to have anticancer effects by suppressing the proliferation of leukemic cells [33]. Previously, in a study by Mohamed and Farghaly, the active ingredients that had been shown to have antineoplastic effects were essential amino acids, phenolic acids, lectins, terpenoids, β-glucans, and unsaturated fats. Each active ingredient can affect the expression of different miRNAs, which are involved in the pathogenesis of AML [34].

β-glucan is an active ingredient that can increase miRNA122 expression [5]. In AML patients, it was found that miRNA122 expression was decreased. The effect of β-glucan that increases miRNA122 expression suppresses the over-activated PLK-1 pathway. Thus, the excessive cell cycle can be suppressed and AML cell proliferation can be controlled [18].

Lectin can regulate miRNA133 expression. Normally, miRNA133 regulates EGFR so that its number is not excessive. However, in AML patients, miRNA133 expression decreased, followed by an increase in the number of EGFR. Lectins can increase miRNA133 expression which can reduce EGFR in AML cells [22, 29]. In addition, miRNA133 can also reduce the Evi 1 receptor whose expression is associated with worsening the prognosis of AML patients [31].

Phenolic acids in the form of resveratrol and terpenoids in the form of ursolic acid have the effect of reducing miRNA21 expression. In AML patients, miRNA21 causes resistance to chemotherapy agents, such as cytarabine and daunorubicin. This resistance occurs due to the decreased activity of PDCD4 and ARL2, which normally act as tumor suppressors in AML patients [21, 23]. In addition, miRNA21 also increases AML cell proliferation by inhibiting the BCL11B pathway. This pathway plays an important role in reducing the expression of oncogenes, such as HDM2 or MDM2, which causes inactivation of the p53 pathway [22]. Phenolic acid and terpenoids administration can reduce the expression of miRNA21, so that the chemoresistance and proliferation of AML cells also decreases.

Besides miRNA21, phenolic acid can also inhibit the expression of miRNA155. By reducing miRNA155 expression, phenolic acid can activate the FOXO3 pathway which acts as a tumor suppressor [26]. The pathway that is also the target of miRNA155 is PI3K/Akt. Elevated miRNA155 expression is followed by the activation of the Akt pathway that supports AML cell survival [3].

Long chain polyunsaturated fatty acids (LCPUFA) can increase miRNA146 expression [16]. miRNA146 is an important tumor suppressor that can reduce leukemic cell proliferation and increase sensitivity to chemotherapy. The pathway that is the target of miRNA146 is the CXCL12/CXCR4 pathway. miRNA146 decreases the activity of this pathway, thereby increasing the migration of hematopoietic stem cells that are used to treat AML patients [35]. If overactivated, the CXCR4 pathway can increase chemoresistance and cause a worsening of the prognosis in AML patients [3].

Pleurotus ostreatus has the potential to be a complementary therapy for AML. This potential lies in the content of active ingredients that can regulate the expression of certain miRNAs. These miRNAs, in turn, work through pathways that affect the proliferation and apoptosis of leukemia cells. The findings regarding the association of the active ingredient in *Pleurotus ostreatus* with miRNA expression that influences proliferation and apoptosis in AML can be a beneficial information to researchers, health practitioners, and pharmaceutical companies to develop AML complementary therapies that are more accessible and effective. In addition, the results of this systematic review can also be used as a reference for medical science and the use of natural ingredients as a complementary therapy for AML.

5. Conclusion

Pleurotus ostreatus, more commonly known as oyster mushroom, is a plant with many benefits, one of which is anti-leukemia. These benefits are obtained from the active ingredients contained in it. From various literatures that have been systematically reviewed, it can be concluded that *Pleurotus ostreatus* has a potential effect as a complementary therapy for acute myeloid leukemia. The active ingredients of *Pleurotus ostreatus* with anticancer properties include *β-glucan*, lectin, phenolic acid, terpenoids, and unsaturated fatty acids. Finally, miRNAs that have the potential to become therapeutic targets for acute myeloid leukemia are miRNA146, miRNA122, miRNA21, miRNA155, and miRNA133.

Compliance with ethical standards

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Disclosure of conflict of interest

All the authors declare no competing interests.

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