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Review

A comprehensive review of phytochemical approaches in treatment of acute myeloid leukemia: Associated pathways and molecular mechanisms

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ABSTRACT

Acute myeloid leukemia (AML) is a type of cancer that affects the blood and bone marrow. This review conducts a thorough analysis of AML, addressing its genetic modification. The examination extends to the current therapeutic approaches employed for AML, shedding light on their efficacy and the notable side effects experienced by patients undergoing these treatments, leading to a low overall survival rate. Therefore, exploring alternative treatments, such as phytochemicals, is necessary. Furthermore, the review explores the complex landscape of phytochemicals, categorizing them based on their diverse properties, which include alkaloids, phenols, terpenoids, organo-sulfur compounds, and other compounds, including quinones, and elucidating their mechanisms of action. Special emphasis is placed on their involvement in critical signaling pathways, with a particular focus on how these phytochemicals impact AML when evaluated across a spectrum of cell lines. This in-depth exploration aims to uncover potential targets within the molecular landscape of AML where phytochemicals can exert their therapeutic effects. The review investigates the potential role of plant-derived phytochemicals as adjunctive therapies for AML. This exploration encompasses the identification of specific phytochemicals that exhibit promising anti-leukemic properties and evaluates their potential in clinical settings. Beyond conventional treatments, the review explores the integration of complementary and alternative medicine as a holistic approach to managing AML. The examination encompasses the synergy between conventional therapies and alternative interventions, exploring how these combined strategies may enhance overall therapeutic outcomes and mitigate side effects. From a forward-looking perspective, the overarching goal is to contribute to the evolving landscape of AML treatment by considering innovative approaches that harness the therapeutic potential of phytochemicals, both independently and in conjunction with established medical interventions.

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1. Introduction

Acute myeloid leukemia (AML) is the second most common hematologic neoplasm, characterized by increased immature blood cells due to inadequate maturation of early myeloid cells and accelerated, heterogeneous cell division (Ilyas et al., 2015; Xu, Chang, Luo, & Zhang, 2023). While specific triggers are often unknown, genetics and environmental factors, such as benzene exposure, play significant roles. Risk factors include a history of myelodysplastic syndromes (MDS), myeloproliferative neoplasms (MPN), and prior radiation or chemotherapy (Carter et al., 2020). AML relies on specific aberrations in signaling pathways (e.g., NF-κB, Wnt/β-Catenin, Hedgehog, Notch, EGFR, JAK/STAT, PI3K/AKT/mTOR, TGF/SMAD, and PPAR pathways) within leukemic stem cells (LSCs) for survival, self-renewal, and growth. Altered metabolic pathways, including glycolysis, oxidative phosphorylation (OXPHOS), amino acid synthesis, and lipid production, are also observed in AML (Rodrigues et al., 2021; Mesbahi, Trahair, Lock, & Connerty, 2022).

For over four decades, the primary approach to AML has been induction therapy, employing intensive chemotherapy (commonly "7 + 3") using cytarabine and anthracycline or daunorubicin to impact DNA replication and apoptotic pathways. However, its tolerability is limited, especially in older and less fit patients (Bhansali, Pratz, & Lai, 2023). Despite a few alternative drugs, the National Cancer Institute reports a 27.4% overall survival rate for AML over five years, partly due to drug resistance and increased susceptibility to other cancers and infections. Current treatment shortcomings drive ongoing efforts to find innovative pharmaceuticals for AML. Phytochemicals, natural compounds derived from plants, are considered important reservoirs for developing new drugs. Various plant-derived compounds, including saponins, alkaloids, phenolics, triterpenes, coumarins, polysaccharides, and anthraquinones, among others, demonstrate anti-tumor effects. These effects are not only due to a direct toxic impact on cancerous cells but also involve the modulation of macrophage phenotypic differentiation and potentially the secretion of cytokines (Miękus et al., 2020). Substantial evidence supports the beneficial roles of bioactive phytoconstituents in treating hematological malignancies. Consequently, research is ongoing to develop new cancer therapies from these traditional compounds or phytochemicals. Notably, substances such as curcumin from *Curcuma longa* L., epigallocatechin gallate from green tea leaves (EGCG), genistein from soybean, quercetin from tomatoes, and resveratrol from grapes and peanuts have been documented for their anti-AML properties (Ersöz & Adan, 2022; Hsiao et al., 2019; Wang et al., 2016a; Westphal, McGeary, Rudloff, Wilke, & Penack, 2017; Zhou, Ning, Zeng, Zhou, & Ding, 2021). Many *in vitro* studies and preclinical research have demonstrated the effectiveness of phytochemicals against AML. Some of these include Maytansinoids, from *Maytenus serrata*, which exhibit cytotoxicity against AML cell lines and have been reported to have an antileukemic effect in phase I and II clinical trials (Shao et al., 2012). Flavopiridol, an alkaloid from *Dysoxylum binectariferum* (Roxb.) Hook. f. ex Bedd., has demonstrated strong antiproliferative properties and exhibited antitumor effects in clinical trials (Zeidner & Karp, 2015). Thus, the promising antileukemic effects of various phytochemicals, demonstrated through numerous *in vitro* and preclinical studies, emphasize their potential as innovative treatments for AML, warranting further research and development.

This article aims to explore the adverse effects associated with conventional therapies for AML and investigate the potential of phytochemicals as either chemo-preventive or phyto-chemotherapy agents in AML treatment. It seeks to identify specific molecular targets and mechanisms within the landscape of AML where phytochemicals may exert therapeutic effects, thus contributing to the evolving treatment strategies for AML, both independently and in conjunction with established medical interventions. All literature searches were conducted over the past 10 years, utilizing databases such as Google Scholar, Web of Science, and PubMed, focusing on journal articles and research reports published in English.

2. Classifications and genetic modifications of acute myeloid leukemia

Prognostic cytogenetic abnormalities, which can be categorized by various chromosomal alterations, are observed in patients diagnosed with AML. The recurring cytogenetic abnormalities involved comprise t (8; 21) (q22; q22.1); Runt-related transcription factor 1 (RUNX1/RUNX1T1), inv (16) (p13.1q22) or t (16;16)/(p13.1q22) core binding factor beta subunit – Myosin heavy chain 11 (CBFB-MYH11); and acute promyelocytic leukemia t (15; 17) (q22, q21) (Döhner et al., 2017). According to Hasserjian (2014), many AML patients display normal karyotypes; however, they develop de novo mutations that carry prognostic significance. These mutations include the fms-like tyrosine kinase 3 (FLT3) gene (FLT3-ITD and FLT3-TKD) as well as mutations in transcription factor genes like CCAAT enhancer binding protein alpha (CEBPα), crucial for differentiation (Daver et al., 2019; Su et al., 2022). Additionally, the nucleophosmin-1 (NPM1) gene and isocitrate dehydrogenase 1/2 (IDH1/IDH2) enzymes (Zarka et al., 2020; Issa & DiNardo, 2021) are also present in AML (Fig. 1). The World Health Organization and the International Consensus Classification have recently updated the classification of AML (Arber et al., 2022; Khoury et al., 2022). It is characterized by various genomic alterations affecting epigenetic modifiers (e.g., DNMT3A, TET2, ASXL1, IDH1/IDH2), signaling pathways (e.g., FLT3, RAS, JAK, KIT), transcription factors (e.g., RUNX1, CEBPA, GATA2), the cohesin complex (e.g., STAG2, RAD21, SMC3, SMC1A), RNA splicing factors (e.g., SF3B1, SRSF2, U2AF1, ZRSR2), the tumor suppressor TP53, and NPM1 (Wachter & Pikman, 2024). These genomic alterations impact gene expression, cell signaling, chromatin structure, RNA splicing, and tumor suppression, influencing the prognosis and treatment response in AML. Epigenetic modifiers control DNA methylation and demethylation, while signaling pathways involve tyrosine kinase receptors and cytokine signaling. Transcription factors and the cohesin complex are essential for hematopoiesis and chromosome segregation. Additionally, alterations in RNA splicing factors

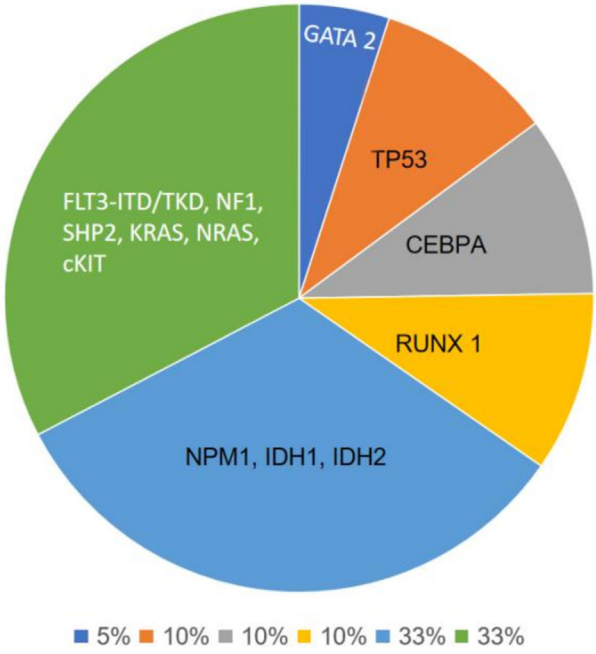


Fig. 1. Common mutations in acute myeloid leukemia.

affect RNA processing (Hou et al., 2020). Hence, treating AML becomes challenging due to various genetic abnormalities. Notably, FLT3, NPM1, and CEBPα genes have been extensively researched for their correlation with both treatment response and the progression of the disease.

3. Current therapeutic approach for AML

The treatment landscape for AML has seen minimal changes over the past four decades. The primary curative approach still involves using the nucleoside analog cytarabine in combination with anthracycline or daunorubicine for induction therapy. After achieving complete remission (CR), patients often undergo multiple cycles of high-dose cytarabine and/or receive an allogeneic stem cell transplant (SCT) (DiNardo & Cortes, 2016). For individuals aged 60 or younger, achieving complete remission is often attainable through this initial cytotoxic induction therapy. Although initial remission may be attainable, treating AML poses persistent challenges, especially in cases involving older patients or when the disease relapses or becomes resistant to treatment (Ramos et al., 2015). In the UK National Cancer Research Institute (NCRI) AML17 trial, 1 206 adults, primarily below the age of 60, underwent random assignment for initial induction therapy. They were given either 60 mg or 90 mg per square meter of body-surface area of daunorubicin. The study revealed no significant disparities in terms of complete response rates or overall survival rates between the two dosage groups (Döhner, Weisdorf, & Bloomfield, 2015). For adults aged 60 years or younger, a favored treatment approach involves administering two to four rounds of intermediate-dose cytarabine. Determining the optimal dosage and the ideal number of cycles continues to be a subject of ongoing inquiry (Döhner, Weisdorf, & Bloomfield, 2015). Elderly individuals diagnosed with AML and exhibiting favorable or intermediate-risk (nonadverse) karyotypes achieve complete remission rates of up to 60% following cytarabine- and anthracycline-based treatment. In contrast, older AML patients with adverse karyotypes experience remission rates as minimal as 20%, coupled with an overall survival period ranging between two and three months (Wang, 2014). In 2017, the FDA approved new drugs, including Midostaurin, Enasidenib, Vyxeos®, and Gemtuzumab ozogamicin, which marked significant advancements in AML treatment (Wei & Tiong, 2017). Venetoclax, Glasdegib (Daurismo), Ivosidenib, and gilteritinib also received approval as standalone treatments for refractory and relapsed AML in 2018) (Dugan et al., 2017; Iyer et al., 2022; DiNardo et al., 2018; Shimony et al., 2022). Incorporating Midostaurin into standard induction chemotherapy regimens was prompted by a rise in cardiac adverse events observed, particularly among older patients. Enasidenib, an IDH1 inhibitor, effectively inhibits the production of 2-HG and promotes the differentiation of myeloblasts, but it yields only a complete remission or complete remission with incomplete hematologic recovery (CR/CRi) rates ranging from 21% to 43% in the initial treatment of AML (Tiong & Wei, 2019). Thus, despite the introduction of new drugs, the prognosis remains poor due to the persistence of therapeutic resistance in known cases, which leads to side effects including toxicities. The commonly used drugs in the treatment of AML and their associated side effects were shown in Fig. 2 (DiNardo et al., 2018; Crossnohere, 2019). FLT3 inhibitors like midostaurin and quizartinib may induce fever, reduced white blood cell levels, nausea, vomiting, and loss of appetite. Notably, differentiation syndrome is a potential side effect, manifesting as fever, respiratory issues, dizziness, or decreased urination (Chen et al., 2019). Anthracyclines, exemplified by daunorubicin, may elevate the risk of heart muscle injury or chronic heart failure. Chemotherapy drugs like cytarabine may result in various effects on the gastrointestinal, hematologic, nervous, respiratory, skin, eye, and cardiovascular systems (Wang & Baron, 2020).

4. Major phytochemicals and acute myeloid leukemia

Phytochemicals are natural compounds derived from plants, generated as secondary metabolites, particularly in response to environmental stress. Numerous phytochemicals found in plants have significantly contributed to advancements in research and the pharmaceutical industry, adding substantial value to both domains. Major phytochemicals include alkaloids (nitrogen-containing compounds), phenols (including flavonoids), terpenoids, organo-sulfur compounds, and other compounds, including quinones. In the past decade, approximately 13 alkaloids have been identified, which include jerantinine B, epiberberine, canthin-6-one, 3,10-dibromofascaplysin, homoharringtonine, curine, tetrandrine, piperlongumine, α–tomatine, cytisine-E, cathachunine, cimicifoetones A and B, 2,2-bis(6-bromo-3-indolyl), and ethylamine. The mechanisms of action include triggering various signaling pathways (c-Jun/JNK, p38, ASK-1), generating reactive oxygen species (ROS), and causing mitochondrial dysfunction, which results in apoptosis and cell cycle arrest. Growth inhibition and differentiation are encouraged by suppressing lysine-specific histone demethylase 1 (LSD1), with enhancement of Notch1 signaling and NF-κB pathways, and downregulation of Notch2. Apoptosis is also promoted by caspase activation, PARP cleavage, and the suppression of anti-apoptotic proteins. Also, 14 major flavonoids have been found effective against AML, which include quercetin, hispidulin, luteolin, gardenin B, oroxylin A, sophoraflavanon G, fisetin, hesperetin, myricitrin, vitisin B, morin, diosmetin, 8-hydroxydaidzein, naringenin, gallic acid, and phenolic compounds, other than flavonoids including hispolon, miconidine acetate, emodin, justicidin B, 20-hydroxyecdysone. Polyphenols induce apoptosis and cell cycle arrest through various mechanisms, such as generating ROS, activating caspases, and causing mitochondrial dysfunction. They lower the levels of anti-apoptotic proteins like Bcl-2, increase pro-apoptotic proteins like Bax, and influence gene expression pathways, including NF-κB, inhibitor of DNA binding

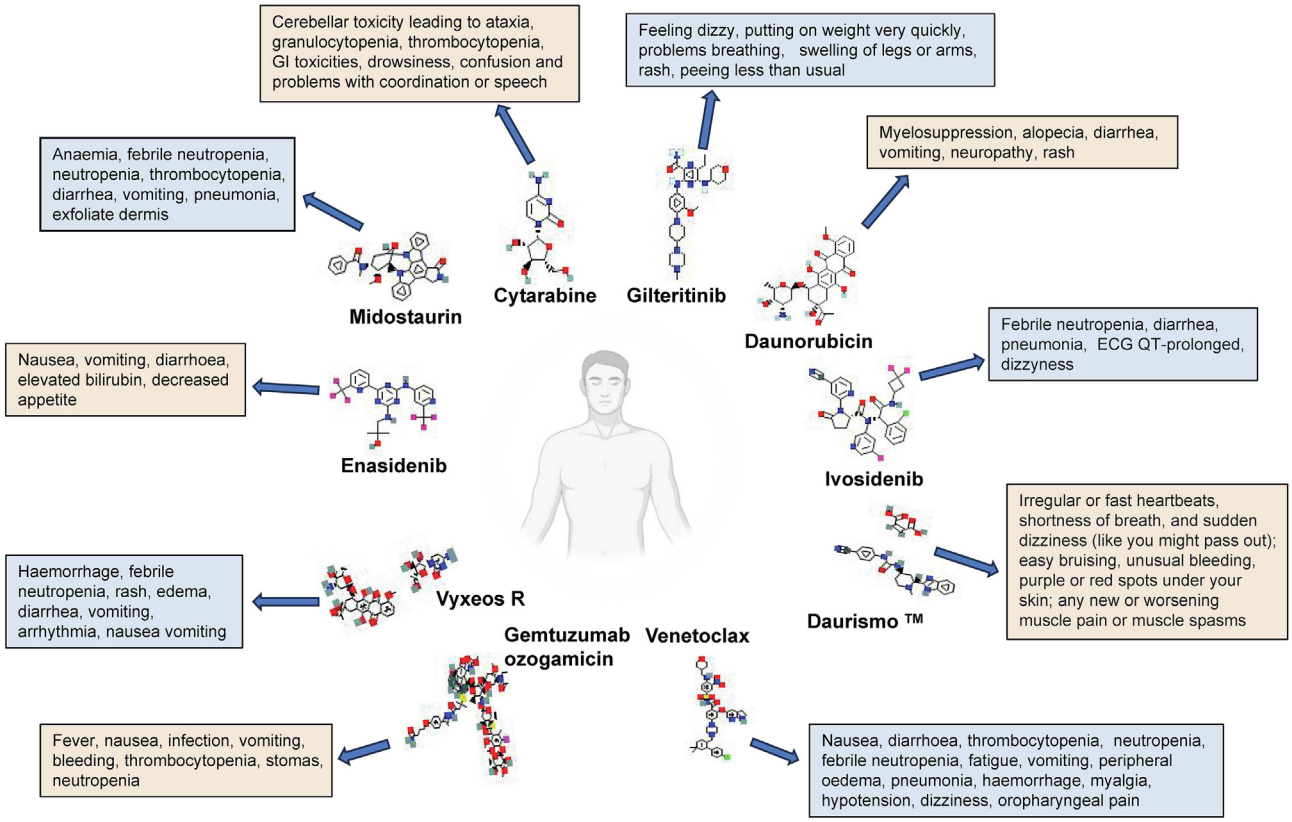


Fig. 2. Common drugs used in the treatment of AML and associated side effects.

(ID), and eukaryotic translation elongation factor 1 alpha 1 (EEF1A1). Additionally, polyphenols inhibit cell proliferation by targeting cell cycle regulators, resulting in arrest at G_0/G_1 or G_2/M phases, and further induce apoptosis through processes like DNA fragmentation, histone acetylation, and modulation of specific signaling pathways. Many terpenes and terpenoids are also having anti-cancer properties. Six major terpenes and terpenoids found effective against AML include dehydroleucodine, betulinic acid, celastrol, friedelin, oridonin, and davanone. Terpenes and terpenoids induce apoptosis and cell cycle arrest by inhibiting NF-κB, downregulating hypoxia-inducible factor 1 subunit alpha (HIF1α), and generating ROS, which causes DNA damage. They disrupt myeloblastosis (Myb) and CCAAT/enhancer binding protein-beta (C/EBPβ) interactions with p300, reduce phosphorylated – mitogen-activated protein kinases (p-MEK) and phosphorylated extracellular signal-regulated kinase (p-ERK) levels, and lead to decreased cell proliferation. Additionally, they cause a drop in mitochondrial membrane potential (MMP) and further increase ROS. Apart from these phytochemicals, organo-sulfur compounds have also been identified as effective against AML, including asterosaponin, and sulforaphane (SFN). It triggers apoptosis and inhibits cell proliferation by suppressing the phosphatidylinositol 3-kinase/ protein kinase B (PI3K/AKT) and extracellular signal-regulated kinase (ERK) 1/2 signaling pathways, along with the c-myc oncogene. They facilitate apoptosis by influencing Bax, Bcl-2, and caspase-3 levels. This overall mechanism results in a marked reduction in cell proliferation.

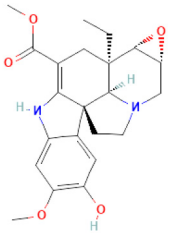
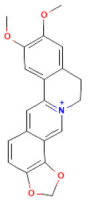
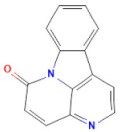
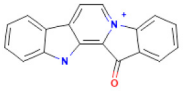
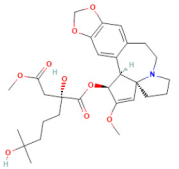
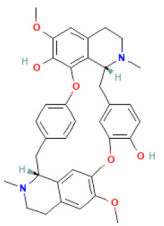
These phytochemicals have shown promise as therapeutic agents for AML. They have been shown to induce apoptosis, inhibit leukemia cell proliferation, modulate signaling pathways essential for cancer progression, and change gene expression patterns linked to the onset and progression of leukemia. Their diverse mechanisms of action make them promising candidates for future cancer therapies.

4.1. Alkaloids

Alkaloids constitute a category of nitrogen-containing organic compounds present in various organisms such as plants, fungi, bacteria, and other living entities (Yang et al., 2023). Alkaloids play a potential role in combating cancer by inhibiting the topoisomerase enzyme, which is crucial for DNA replication. They induce apoptosis, regulate various intracellular targets, and modulate signaling pathways involved in this process (Mondal et al., 2019). It is found that jerantinine B, one of the alkaloids, has cytotoxic effects on AML cells for the first time and highlights the predominant mechanism of action as ROS-induction leading to the activation of the c-Jun signaling pathway, which promotes apoptosis (Alhuthali, Bradshaw, Lim, Kam, & Seedhouse, 2020). Apart from c-Jun activation, a novel LSD1 inhibitor, epiberberine, demonstrated the capability to stimulate the expression of CD86, CD11b, and CD14 in THP-1 and HL-60 cells. LSD1 inhibition leads to epigenetic reprogramming that supports the differentiation of AML cells (Li et al., 2020).

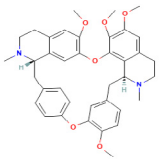
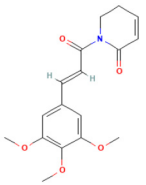
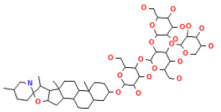
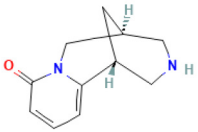
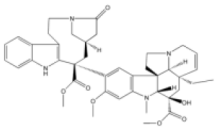
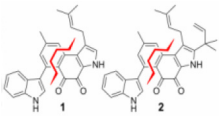
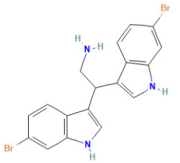
The function of ROS and caspase in cancer studies has proven to be a compelling and intriguing area of investigation. Canthin-6-one, which was first isolated from *Pentaceras australis* Hook. F., and piperlongumine from *Piper longum* L. also had a promising anti-leukemic effect through ROS-induced apoptosis. ROS generation disrupts mitochondrial function, triggering apoptotic pathways (Vieira Torquato et al., 2017; Xiong et al., 2015). 3,10-dibromofascaplysin, curine, and cathachunine are natural alkaloids

Table 1
Alkaloids with anti-AML effect.

Biochemical	Source	Mechanism of action	Study model	Pathway	Molecular structure	References
Jerantinine B	*Tabernaemo-ntana corymbose* Roxb.ex Wall.	Activation of c-Jun/JNK signaling via ROS generation	MV4–11	MAPK signaling pathway.		Alhuthali, Bradshaw, Lim, Kam, & Seedhouse, 2020
Epiberberine	*Coptidis Rhizoma*	Promotes growth inhibition and differentiation through the suppression of LSD1	HL-60, KG1a Cell lines, Patient samples	PI3Kinase pathway		Li et al., 2020
Canthin-6-one	*Pentaceras australis* (F. Muell.) Benth.	p38, JNK and ASK-1 activation, lysosomal AO release, loss of Ψm, increase in ROS	THP-1, HL-60 cell lines	MAPK pathway		Vieira Torquato et al., 2017
3,10-Dibromofascaplysin	*Fascaplysinopsis reticulata* (Hentschel, 1912)	Promotes apoptosis, inhibits cell cycle progression, activates KIT, CTNNB1, CCNE1, NFKB1, and E2F1 expression, and downregulates CCND2, CCNA1, and FLT3 gene expression	Kasumi-1 Cell lines.	MAPK pathway/ Notch pathway		Spirin et al., 2021
Homoharringtonine	*Cephalotoxus fortune* Hook.	Enhancement of the NF-κB pathway as well as P53, upregulated Notch1 and downregulated Notch2	U937 cells, MV4;11, THP-1, K562 Cell lines	Notch pathway		Tan, Zhang, Yuan, Chen, & Wu et al., 2019
Curine	*Chondrodendron platyphyllum* (A.St.-Hil.) Miers	Initiation of cell cycle cessation at the G1 phase, depolarization of the mitochondrial potential and apoptosis	TF-1, Kasumi-1, THP-1, KG-1Cells and HEL cells; Patient MNC	Apoptotic pathway		Dantas et al., 2015

(*continued on next page*)

Table 1 (*continued*)

Biochemical	Source	Mechanism of action	Study model	Pathway	Molecular structure	References
Tetrandrine	*Stephaniae Tetrandrae Radix*	Suppresses NB4 cell proliferation and prompts differentiation linked with autophagy. by ROS accumulation and Notch1 signaling activation	HL-60, K562, and HT-29 Cell lines and (PBMC)	ROS and Notch1 signaling pathways		Liu et al., 2015
Piperlongumine	*Piper longum* L.	Increased ROS levels increased the apoptotic protein expression, autophagic protein, and phosphorylation of p38 and JNK	NB4 Cell lines (*in vivo* and *in vitro*)	ROS-p38/JNK pathways		Xiong et al., 2015
α-Tomatine	*Lycopersicon esculentum* Mill.	Interaction with cholesterol and the disruptive effect on the cell membrane induces apoptosis	Bone marrow sample [BM] HL-60 cells, HL-60 xenografts	NF-κb induced apoptotic pathway		Huang et al., 2015
Cytisine-E	*Citrus grandis* Osbeck and *Citrus paradise* Macf	Caspase activation-mediated apoptosis by inducing ROS-mediated mitochondrial dysfunction by JNK activation	HL-60 cells	ROS/JNK dependent mitochondrial apoptotic pathway		Murata et al., 2020
Cathachunine	*Catharanthus roseus* (L.)	Cell cycle arrest in the S phase induces apoptosis	HL60,K562 leukemia cells	Intrinsic apoptotic pathway		Wang et al., 2016b
Cimicifoetones A and B	*Cimicifuga foetida* L.	Increased the expression of active caspase 3, −8, and −9, Inhibitory effect on proliferation, PARP cleavage	HL 60 Cell lines	Extrinsic pathway, and intrinsic pathway		Zhou et al., 2017
2,2-Bis(6-bromo-3-indolyl) ethylamine	*Didemnum candidum*	Caspase-3 activation and cleavage of PARP-1, suppress anti-apoptotic protein of the Bcl-2 family	U937 cell line	Intrinsic apoptotic pathway		Salucci et al., 2018

(Source: Molecular Structure from https://pubchem.ncbi.nlm.nih.gov/).

that induce apoptosis through cell cycle arrest using apoptotic pathways (Dantas et al., 2015; Spirin et al., 2021; Wang et al., 2016b). Curine induces cell cycle arrest in the G_1 phase, whereas cathachunine arrests in the S phase. These compounds disrupt cell cycle regulation, leading to cell death. Homoharringtonine and 3,10-dibromofascaplysin operate through the Notch signaling pathways, leading to the upregulation of the NF-κB pathway and P53. The former upregulates Notch1 and downregulates Notch2, while the latter activates the expression of (receptor tyrosine kinase) KIT, (Catenin beta 1) CTNNB1, (Cyclin E1) CCNE1, (Nuclear factor kappa B subunit 1) NFKB1, and (Early region 2 binding factor) E2F1, and simultaneously downregulates (cyclin D2) CCND2, (cyclin A1) CCNA1, and FLT3 gene expression (Tan, Zhang, Yuan, Chen, & Wu et al., 2019; Sirin et al., 2021). Tetrandrine, isolated from *Stephania tetrandra* S. Moore, a medicinal herb, suppresses NB4 cell proliferation and promotes autophagy-associated differentiation by the accumulation of ROS and the activation of Notch1 signaling, disrupting cellular homeostasis (Liu et al., 2015). α–Tomatine interacts with cholesterol present on the cell membrane, causing a disruptive effect on the membrane and leading to the induction of apoptosis through the NF-κβ-induced apoptotic pathway, which is a key regulator of immune response and cell survival (Huang et al., 2015). Citbismine-E, on the other hand, initiates caspase activation, leading to apoptosis through the induction of mitochondrial dysfunction mediated by ROS (Murata et al., 2020). Both cimicifoetones A and B, and 2,2-bis(6-bromo-3-indolyl) ethylamine (BrBIn), demonstrate caspase activation, proliferation downregulation, PARP cleavage, and Bcl-2 downregulation through the extrinsic and intrinsic pathways (Zhou et al., 2017; Salucci et al., 2018). Thus, a diverse array of alkaloids, exhibit promising anticancer properties by targeting various cellular mechanisms involved in cancer progression. Their ability to induce apoptosis, regulate signaling pathways, and influence mitochondrial activity underscores their potential as valuable candidates for further exploration in developing novel therapeutic strategies against AML (Table 1).

4.2. Polyphenols

Polyphenols are organic compounds produced solely by plants, exhibiting chemical characteristics associated with phenolic substances. These compounds have demonstrated bioactivities that can regulate oxidative and inflammatory stress, influence macronutrient digestion, and exert effects similar to prebiotics on gut microbiota. Polyphenols can be broadly classified as flavonoids and nonflavonoids, encompassing a wide range of compounds with diverse chemical structures and biological activities.

4.2.1. Flavonoids

Flavonoids are naturally existing compounds in the preliminary stages of a plant's development (Dias et al., 2021). Flavonoids demonstrate diverse anticancer effects by influencing the actions of enzymes engaged in the removal of ROS, playing a role in cell cycle arrest, triggering apoptosis and autophagy, and inhibiting the multiplication and invasive nature of cancerous cells. (Kopustinskiene et al., 2020). Quercetin and myricitrin were observed to trigger apoptosis through the generation of ROS. Quercetin was identified as an activator of the ERK pathway, while myricitrin was found to induce apoptosis by promoting nitric oxide (NO) production, including damage to the cell membrane, nuclear condensation, depletion of superoxide dismutase (SOD), and increased lipid peroxidation. These collective effects ultimately resulted in apoptosis (Lee et al., 2015; Sarkar, Mahapatra & Vadivel, et al., 2020).

Flavonoids have been investigated in the context of AML, specifically focusing on their impact on the activation of caspase-3, a key mediator of apoptosis in leukemia cells. Hispidulin and luteolin from *Salvia plebeia* R. Br. led to an arrest in the cell cycle at Sub G1, and this result arose from the suppression of MAPK-interacting kinase (MNK kinase), leading to a subsequent decrease in the phosphorylation of eukaryotic translation initiation factor 4E (eIF4E). As a consequence of this molecular alteration, apoptosis was induced in AML cells, evident through the cleavage of caspase-3 and PARP (Chen et al., 2020). Sophoraflavanone G and morin, both belonging to the flavonoid class, demonstrate a parallel mechanism of action. They induce DNA fragmentation, activate caspase-3 and caspase-9, downregulate Bcl-2 and Bcl-xL, upregulate Bax, release cytochrome *c* from mitochondria, and cleave PARPs. Together, these actions collectively contribute to the facilitation of apoptosis (Li et al., 2016; Budisan et al., 2017). Gardenin B exhibits cytotoxicity attributed to the methoxy group at C-8. It hinders cell proliferation by causing cell cycle arrest in the G2-M phase and serves as an inducer of apoptosis (Roma et al., 2018). Studies have revealed that c-Jun serves as a crucial transcriptional regulator of the unfolded protein response in AML (Zhou et al., 2017). Furthermore, frequent overexpression of c-Jun has been documented across various genetic subtypes of AML (Zhou et al., 2017). Vitisin B is one of the flavonoids found to have reduced cell proliferation and induces a series of molecular events associated with apoptosis (Wu et al., 2013). This includes the cleavage of caspase-3, caspase-8, caspase-9, PARP1, and the proapoptotic Bax protein. Additionally, vitexin leads to elevated phosphorylation of c-Jun *N*-terminal kinase (JNK) and increased expression of Fas ligand (FasL). Diosmetin triggers apoptosis in AML cells by activating estrogen receptor beta (ERβ) and inducing TNFα-mediated apoptosis (Roma, Rota & Spanuolo et al., 2018). This effect is associated with the activation of caspases-8 and 3/7 and the death-inducing cytokine (Tumor Necrosis Factor-alpha) TNF-α.

Flavonoids have also been associated with epigenetic modulation, including the downregulation of specific genes involved in AML. The diverse pharmacological activities of flavonoids, such as their impact on gene transcription and epigenetic mechanisms, make them a subject of interest for potential cancer therapy. Oroxylin A extracted from *Oroxylum indicum* (L.) Kurz exhibits diminished NBT activity, decreased CD11b/CD14 expression, and lower levels of Histone deacetylase 1(HDAC-1), resulting in a reduction in RUNX1/RUNX1T1 fusion protein expression and an increase in histone acetylation (Hui et al., 2016). Fisetin and hesperetin were found to exert varied impacts on AML cells, leading to cell cycle arrest and alterations in signaling pathways. This manifested as inhibited proliferation and the induction of G_2/M arrest. Microarray gene profiling analysis uncovered modifications in the mitogen-activated protein kinase (MAPK) and ID signaling pathways, as well as changes in numerous genes associated with cell proliferation, cell division, and apoptosis (Adan & Baran, 2015). Recently, 8-hydroxydaidzein and naringenin have demonstrated anti-proliferative effects along with the downregulation of genes associated with AML (Wu, Wang, Hsu, Yen & Wu., 2023; Wen, Lu, Sun, Li, Liao & Li., 2023). The suppression of mitochondrial activity has been extensively investigated as a potential anticancer strategy. The inhibition of mitochondrial respiration by gallic acid relies on its ability to inhibit protein kinase B (AKT)/mammalian target of rapamycin (mTOR), Akt/mTOR signaling (Gu, Zhang, Meng, Xu & Xie, 2018). Thus, flavonoids exhibit significant potential as anticancer agents in AML through diverse mechanisms, including apoptosis induction, cell cycle arrest, enzyme modulation, and epigenetic regulation (Table 2).

4.2.2. Nonflavonoids

Nonflavonoids include various polyphenolic compounds such as phenolic acids, stilbenes, lignans, and other classes, each characterized by distinct chemical structures and biological properties.

Table 2
Polyphenols with anti-AML effect.

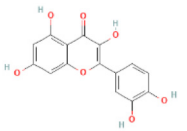
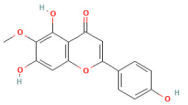
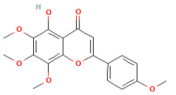
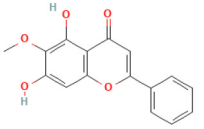
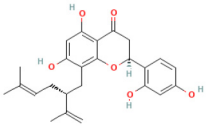
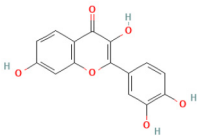
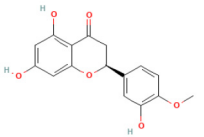
Biochemical	Source	Mechanism of action	Study model	Pathway involved	Molecular structure	References
Flavanoid Quercetin	*Fagopyrum esculentum*	Induces ROS-mediated ERK activation	THP-1, MV4-11, and U937	ROS-ERK Pathway		Lee et al., 2015
Hispidulin luteolin	*Salvia plebeia*	Elevated Sub-G1 DNA content results from reduced eIF4E phosphorylation via MNK kinase suppression, leading to AML cell apoptosis through caspase-3 and PARP cleavage	MOLM-13 and MV4-11	Extrinsic and intrinsic apoptotic pathways		Chen et al., 2020
Gardenin B	*Baccharis scandens* Pers.	Cytotoxic as methoxy group at C-8, Blocks proliferation by arresting the cells in the G2-M phase and is an apoptotic inducer.	HL-60 and U-937 cells, human peripheral blood mononuclear cells.	Extrinsic and intrinsic apoptotic pathways.		Cabrera et al., 2016
Oroxylin A	*Oroxylum indicum*	Reduced NBT activity, CD11b/CD14 expression, and down-regulated HDAC-1 levels led to decreased AML1/ETO fusion protein expression and enhanced histone acetylation	t(8;21)-positive Kasumi-1 and primary AML cells	proteasome-dependent pathway		Hui et al., 2016
Sophoraflavanon G	*Sophora flavescens* aiton.	DNA fragmentation, caspase-3, and caspase-9 activation, downregulation of Bcl-2 and Bcl-xL, upregulation of Bax, cytochrome *c* from mitochondria, cleavage of PARPs, collectively facilitating apoptosis	HL-60 cells	Mitochondrial-mediated pathways, and the MAPK pathway		Li et al., 2016
Fisetin	*Fragaria* × *ananassa* Duch.	Downregulation of genes such as ID1, ID3, IDH1 and LONP1 expression	HL60 cells	ID signaling pathway, MAPK signaling pathway, cell cycle pathway, JAK/STAT signaling pathway, PI3K/AKT signaling pathways. and cell cycle checkpoint pathways		Adan & Baran, 2015
Hespertin	*Citrus limon* (L.)	SPRR2D, MT1F, and SASH1 upregulation, Downregulation of RPS6P1, RPS9, and RPS25, downregulation of both CMYC and PIM1 by EEF1A1, growth inhibition and apoptosis	HL60 cells	ID signaling pathway, eukaryotic ribosome and translation-related networks, and TGF-β and MAPK pathways		Adan & Baran, 2015

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Table 2 (*continued*)

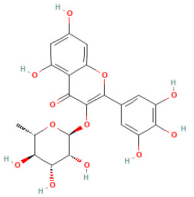
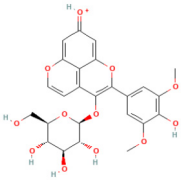
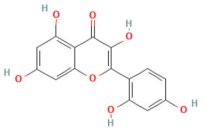
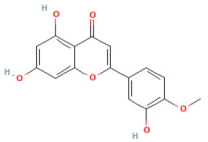
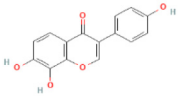
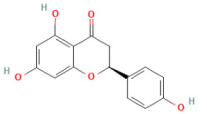
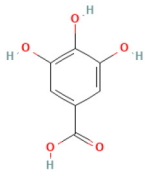
Biochemical	Source	Mechanism of action	Study model	Pathway involved	Molecular structure	References
Myricitrin	*Madhuca longifolia* latifolia (Roxb.)	Cytotoxicity by ROS and nitric oxide (NO), leads to cell membrane damage, nuclear condensation, decreased superoxide dismutase (SOD) levels, and heightened lipid peroxidation	HL-60	Apoptotic pathway		Sarkar, Mahapatra & Vadivel, 2020
Vitisin B	*Vitis thunbergii* var. *taiwaniana*	Inhibition of cell proliferation, cleavage of caspase-3, caspase-8, caspase-9, PARP1, and the proapoptotic Bax protein., elevations in the phosphorylation of c-Jun N-terminal kinase (JNK) and the expression of Fas ligand (FasL)	HL-60	JNK signaling pathway		Wu et al., 2013
Morin	*Maclura pomifera* (Raf.) Schneid.	Induces caspase-dependent apoptosis, concurrently impacting mitochondrial membrane potential, resulting in cytochrome *c* release, inhibiting Bcl-2 expression, and activating Bax proteins.	HL-60	Intrinsic apoptotic pathways, Akt pathways		Budisan et al., 2017
Diosmetin	*Petroselinum crispum* (Mill.) Nym.	Induced apoptosis that was mediated by ERβ and TNFα	OCI-AML2 cell line, *in vivo* study (immunodeficient mice)	extrinsic apoptotic pathway, NF-κB signaling		Roma, Rota & Spanuolo, 2018
8-Hydroxydaidzein	*Glycine* max (L.) Merr.	Downregulation of differentially expressed genes (DEGs), CCND2, MYC, NPM1, FLT3, and TERT,	U-937, THP-1, and HL-60	rRNA processing and ribosome biogenesis pathways		Wu, Wang, Hsu, Yen & Wu, 2023
Naringenin	*Citrus* × *aurantiifolia* (Christm.) Swingle	Downregulation of lncRNA XIST/miR-34a/HDAC1 axis	HL60, THP-1 cells and KG-1 AML cell lines	PI3K/AKT signaling, forkhead box signaling, p53 signaling, and Ras signaling		Wen, Lu, Sun, Li, Liao & Li, 2023
Gallic acid	*Vaccinium corymbosum* L.; *Quercus infectoria* Oliv.	Mitochondrial malfunction, energy depletion, and AML cell apoptosis	THP-1, MV411 cell lines and MNC and CD34 cells.	Akt/mTOR pathway		Gu, Zhang, Meng, Xu & Xie, 2018

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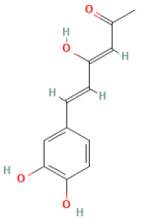
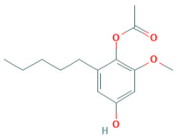
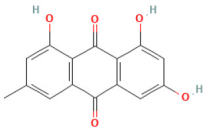
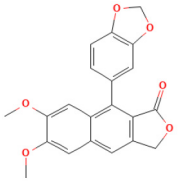
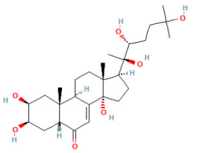
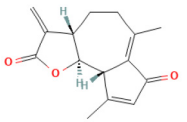
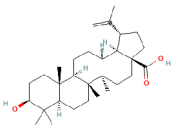
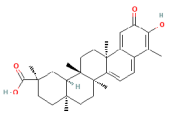
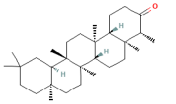
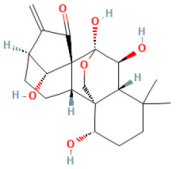
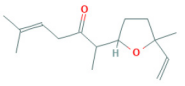
Table 2 (*continued*)

Biochemical	Source	Mechanism of action	Study model	Pathway involved	Molecular structure	References
Phenolic compounds (other than flavonoids)						
Hispolon	*Phellinus linteus*	Suppress cell growth and promote apoptosis pathways by suppression of Bcl-2 and trigger the activation of JNK1/2 and caspase-8, −9, and −3	THP-1, U937, HL-60, OCI, MV4-11, andMOLM-13 (*in vitro* and *in vivo*)	MAPK, NF-κB pathway, Apoptotic pathway		Hsiao et al., 2013
Miconidine acetate	*Eugenia hiemalis* Cambess.	cytostatic effect, DNA fragmentation, phosphatidylserine exposure and caspase-3 and PARP cleavage, ROS generation	K562 cells	Intrinsic and extrinsic apoptosis pathways		Maioral et al., 2018
Emodin	*Rumex abyssinicus* Jacq.	Downregulate cellular. proliferation. Induce cell cycle arrest in G0/G1 phase and induced 50% apoptosis	HL-60, THP 1, KG-1a	caspase-dependent apoptotic pathway and the Akt and ERK signaling pathways.		Mahbub et al., 2013
Justicidin B	*Linum leonii* F.W.Schultz.	cytotoxic by DNA fragmentation; proapoptotic agent based on caspase-9 and caspase	HL-60	Intrinsic mitochondrial cell death signaling pathways.		Momekov et al., 2014
20-Hydroxyecdysone	Dacrycarpus imbricatus	Cell cycle arrest at G_0/G_1 phase	OCI-AML cell line.	–		Thuy et al., 2017

(Source: Molecular Structure from https://pubchem.ncbi.nlm.nih.gov/).

Table 3
Terpenes and terpenoids with anti-AML effects.

Biochemical	Source	Mechanism of action	Study model	Pathway	Molecular structure	References
Dehydroleucodine	*Gynoxys verrucosa*	Inhibit NF-κb by a significant decrease in phospho-p65	HL-60, Kasumi-1, KG-1, MOLM-13, MV4-11, THP-1, TUR, and U937 cell lines	NF-κB signaling pathway.		Ordóñez et al., 2016
Betulinic acid	*Betula pendula*	Downregulation of the HIF1α pathway and generation of ROS, DNA damage, apoptosis	THP1 cells	HIF1α pathway		Zhang et al., 2017a
Celastrol	*Tripterygium wilfordii* Hook. f.	Affects Myb and C/EBPβ by interrupting their interaction with the transcriptional coactivator p300	QT6, 3 T3-L1 cells	–		Coulibaly et al., 2018
Friedelin	*Azima tetracantha* Lam.	Induction of apoptosis and G2/M cell cycle arrest, protein levels of p-MEK and p-ERK decreased	AML-196 leukemia cells	MEK/ERK and PI3K/AKT signaling pathway		Chang et al., 2020
Oridonin	*Rabdosia rubescens* (Hemsl.), Hara.	Inhibit proliferation and induce cell apoptosis	Cisplatin-resistant human AML subline MV4-11/DDP and MOLM13/DDP cells	–		Zhang et al., 2017b
Davanone	*Artemisia pallens* Walls. ex DC	Caspase-dependent apoptosis, MMP levels sharply dropped, increase in ROS	NCI-H526 cells and AML-193 cell line	PI3K/AKT/MAPK signaling pathway		Xiao, Deng & Wang, 2020

(Source: Molecular structure from https://pubchem.ncbi.nlm.nih.gov/).

Miconidin acetate (MA) is a compound derived from hydroquinone that has been isolated from *Eutypella hiemalis*. MA results in reduced cell proliferation, increased generation of ROS, and the initiation of both intrinsic and extrinsic apoptosis pathways. Consequently, it induces mitochondrial damage, triggering the release of proapoptotic mitochondrial proteins, activating caspase-3 and PARP, and causing DNA fragmentation (Maioral et al., 2019). Emodin, an anthraquinone, has shown cell cycle arrest at the G_0/G_1 phase and induced apoptosis through caspase-dependent apoptotic pathways and the suppression of Akt and ERK signaling pathways (Chen et al., 2018). Justicidin B, a lignan, is found to cause apoptosis by using the intrinsic pathway of apoptosis (Momekov et al., 2014). 20-hydroxyecdysone is a steroid that induces cell cycle arrest at the G_0/G_1 phase (Thuy et al., 2017), whereas the underlying molecular mechanism and the pathway involved are not clear yet.

4.3. Terpenes and terpenoid

Terpenes and terpenoids are widely distributed in the plant kingdom and contribute to the characteristic scents and flavors of many fruits, flowers, and herbs. Moreover, these compounds have found applications in traditional medicine, perfumery, and the pharmaceutical industry due to their diverse biological activities and therapeutic potential, among which is their notable anticancer potential (Perveen & Al-Taweel, 2018). Terpenes are recognized for their uncomplicated hydrocarbon structures. Conversely, terpenoids constitute a modified category of terpenes, encompassing hydrocarbons with the addition of oxygen. The distinction lies in the modifications undergone by terpenoids, frequently involving the introduction of functional groups or the repositioning/removal of oxidized methyl groups at distinct positions within the molecular structure (Perveen & Al-Taweel, 2018). Around six terpenes and terpenoids have been identified as effective against AML over the past decade. One such terpenoid, dehydroleucodine, a terpenoid, proficiently hinders NF-κB by causing a significant decrease in phospho-p65 levels (Ordóñez et al., 2016). Betulinic acid is a triterpene that has shown elevated expression of the Aryl hydrocarbon receptor (AHR) by demethylating the AHR promoter in AML cells. This heightened AHR expression then interacts with and captures ARNT, resulting in the suppression of the hypoxia-inducible factor-1α (HIF1α) pathway (Zhang et al., 2017a). The pentacyclic triterpenoid celastrol is found to inhibit the cellular proliferation of leukemia cells (Coulibaly et al., 2018). Friedelin, another triterpenoid, significantly inhibited human leukemia growth through apoptosis induction (Chang et al., 2020). It also hindered AML196 leukemia cell migration and invasion by blocking the MEK/ERK and PI3K/AKT signaling pathways, like davonone, a terpenoid that was extracted from *Artemisia pallen.* Oridonin, extracted from *Rabdosia rubescens*, is a diterpenoid known for its robust anticancer properties (Xiao, Deng & Wang et al., 2020). Oridonin as well as davanone stimulate apoptosis and impede cell proliferation in cells resistant to cisplatin in AML cells (Zhang et al., 2017b). The molecular mechanisms and related pathways of terpenes and terpenoids have not been extensively examined or explored to date, and there is a paucity of *in vivo* studies on this topic. So, the diverse roles of terpenes and terpenoids in contributing to the sensory qualities of plants, along with their extensive applications in various industries, underscore their significance. The promising anticancer potential demonstrated by specific terpenoids, such as dehydroleucodine, betulinic acid, celastrol, friedelin, oridonin, and davanone, highlights their therapeutic relevance, yet further research is needed to comprehensively understand the molecular mechanisms and pathways underlying their actions, particularly *in vivo* (Table 3).

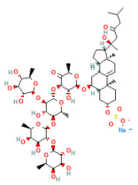
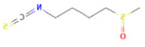
4.4. Organic sulfur

A study showed that compounds containing sulfur inhibited the development of leukemia through various molecular mechanisms (Kim et al., 2014). The onset of apoptosis aligned with the suppression of PI3K/AKT signaling, downregulation of ERK 1/2, MAPK signaling, and a decrease in c-myc expression were observed in AML cells by asterosaponin (Thao et al., 2014). Sulforaphane (SFN) is another organic sulfur that induces apoptosis in AML cell lines by caspase-3-dependent pathways (Wang et al., 2018). Limited research has been conducted on organic sulfur in the context of AML (Table 4).

5. Synergistic effect of phytochemicals on acute myeloid leukemia

The synergistic activity of phytochemicals pertains to the collective impact of different phytochemicals, yielding a more significant outcome than the cumulative effects of each component. This phenomenon has been investigated across diverse areas, including cancer therapy and addressing antimicrobial resistance. A study conducted on THP-1 cells revealed that the combined action of the flavonoids kaempferol and quercetin demonstrated synergistic inhibition of AML cell proliferation. Additionally, these flavonoids were found to upregulate the expressions of Bax, caspase-3, and caspase-8, suggesting a positive regulatory effect on these apoptotic markers (Jafarbeigloo et al., 2021). In addition to the synergistic effects observed between two phytochemicals, the combination of flavonoids with conventional therapeutic drugs has demonstrated encouraging outcomes as well. Coumarin and doxorubicin

Table 4
Organic Sulfur with anti-AML effect.

Biochemical	Source	Mechanism of action	Study model	Pathway involved	Molecular structure	References
Asterosaponin	*Astropecten monacanthus* Sladen, 1883	PI3K/AKT downregulation, ERK 1/2 and c-myc downregulation	HL-60	PI3K/AKT signaling, MAPK signaling.		Thao et al., 2014
Sulforaphane (SFN)	*Brassica oleracea varsabellica*	Bax, Bcl-2 and caspase-3 based apoptosis, reduced cell proliferation	KG1a and K562 cells	Apoptotic pathway		Wang et al., 2018

(Source: Molecular Structure from https://pubchem.ncbi.nlm.nih.gov/).

suppressed Bcl-2 while elevating p53, cleaved caspase-3, and PARP protein expressions (Al-Abbas & Shaer, 2021). Topotecan, along with thymoquinone, has shown antiproliferative and apoptotic effects (Khalife et al., 2014). A recent study has shown the combination of azacitidine and selinexor exhibited a synergistic anti-leukemia effect in acute myeloid leukemia by targeting c-Myc signaling (Long et al., 2023). In a preliminary study using an MDR AML cell line HL-60R and a flow cytometry assay, it was observed that curcumin increases the intracellular accumulation of doxorubicin, similar to the P-gp inhibitor verapamil (Labbozzetta et al., 2023). Thus, curcumin may also modulate P-gp function in AML cells. The study of synergistic interactions among phytochemicals, both in combination with each other and with conventional therapeutic drugs, holds promising implications for enhancing anti-leukemic effects and regulating key apoptotic markers, highlighting the potential of these synergies in advancing therapeutic strategies for AML.

6. Discussion and prospects

Cancer, an intricate ailment with diverse origins, is commonly tackled through traditional treatments, often accompanied by considerable challenges and substantial financial burdens. Acute myeloid leukemia poses challenges in finding effective therapies with high relapse rates. A reduced survival rate is partly linked to drug resistance and an increased vulnerability to subsequent cancers and infections. While conventional chemotherapies are potent, they come with notable side effects. As in the review, there is a growing interest in integrating phytochemical-based complementary alternative medicine, primarily due to its capacity to selectively target various molecular pathways while minimizing toxic effects. Phytochemicals target AML by influencing essential pathways such as PI3K/AKT, MAPK (including ERK, JNK, and p38 pathways), and apoptosis, enhancing mechanisms that induce cancer cell death. They also modulate NF-κB signaling and pathways related to ROS, regulating cell survival and responses to oxidative stress. These interactions highlight their promise as natural therapeutic agents for AML, effectively targeting key pathways in cancer biology. Thus, the integration of diverse phytochemicals into cancer therapy offers a flexible approach that adeptly coordinates a variety of molecular signaling processes. The combination of cytotoxic agents with phytochemical inhibitors results in a synergistic blend of inhibitory actions against AML. While the amalgamation of traditional and alternative modalities holds promise in therapy, further clinical integration is necessary for more effective and less aggressive treatments.

The interaction between phytochemicals and chemotherapy drugs highlights both promise and challenges in cancer treatment. Phytochemicals such as flavonoids, known for their antioxidant activity, have the potential to interfere with the effectiveness of certain chemotherapy drugs. Despite their promising attributes for cancer treatment, challenges such as low solubility in some phytochemicals, poor permeability, and short biological half-life limit their application. The pharmacological effects of other drugs can be significantly altered by the simultaneous use of phytochemicals and their metabolites. Further research is needed to overcome these challenges and harness the potential of naturally available chemopreventive drugs for the treatment of AML in clinical settings.

The insights derived from this review on phytochemicals and AML contribute valuable information to the field by enhancing our understanding of the potential role of plant-derived compounds in AML treatment. This knowledge adds value by providing researchers and clinicians with new perspectives on therapeutic approaches. It may guide further investigations into the development of novel treatments or combination therapies involving phytochemicals. Additionally, the review could inspire the exploration of alternative and complementary strategies for managing AML, broadening the therapeutic options available for patients. We look forward to future research that can expand upon the current understanding of phytochemicals and their potential role in improving AML treatment.

CRediT authorship contribution statement

Mouvanal Sajana: Writing – original draft. **T.S. Gopenath:** Writing – review & editing. **Basalingappa M. Kanthesh:** Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Structures of potential anti-acute myeloid leukemia phytochemicals (Tables 1.1, 1.2, 1.3, 1.4).

Supplementary data to this article can be found online at https://doi.org/10.1016/j.chmed.2024.11.010.

References

Adan, A., & Baran, Y. (2015). The pleiotropic effects of fisetin and hesperetin on human acute promyelocytic leukemia cells are mediated through apoptosis, cell cycle arrest, and alterations in signaling networks. *Tumour Biology, 36*(11), 8973–8984.

Al-Abbas, N. S., & Shaer, N. A. (2021). Combination of coumarin and doxorubicin induces drug-resistant acute myeloid leukemia cell death. *Heliyon, 7*(3) e06255.

Alhuthali, H. M., Bradshaw, T. D., Lim, K. H., Kam, T. S., & Seedhouse, C. H. (2020). The natural alkaloid Jerantinine B has activity in acute myeloid leukemia cells through a mechanism involving c-Jun. *BMC Cancer, 20*(1), 629.

Arber, D. A., Orazi, A., Hasserjian, R. P., Borowitz, M. J., Calvo, K. R., Kvasnicka, H. M., Wang, S. A., Bagg, A., Barbui, T., Branford, S., Bueso-Ramos, C. E., Cortes, J. E., Cin, P. D., DiNardo, C. D., Dombret, H., Duncavage, E. J., Ebert, B. L., Estey, E. H., Facchetti, F., ... Tefferi, A. (2022). International consensus classification of myeloid neoplasms and acute leukemias: Integrating morphologic, clinical, and genomic data. *Blood, 140*(11), 1200–1228.

Bhansali, R. S., Pratz, K. W., & Lai, C. (2023). Recent advances in targeted therapies in acute myeloid leukemia. *Journal of Hematology & Oncology, 16*(1), 29.

Budisan, L., Gulei, D., Zanoaga, O. M., Irimie, A. I., Sergiu, C., Braicu, C., Gherman, C. D., & Berindan-Neagoe, I. (2017). Dietary intervention by phytochemicals and their role in modulating coding and non-coding genes in cancer. *International Journal of Molecular Sciences, 18*(6), 1178.

Cabrera, J., Saavedra, E., del Rosario, H., Perdomo, J., Loro, J. F., Cifuente, D. A., Tonn, C. E., García, C., Quintana, J., & Estévez, F. (2016). Gardenin B-induced cell death in human leukemia cells involves multiple caspases but is independent of the generation of reactive oxygen species. *Chemico-Biological Interactions, 256*, 220–227.

Carter, J. L., Hege, K., Yang, J., Kalpage, H. A., Su, Y., Edwards, H., Hüttemann, M., Taub, J. W., & Ge, Y. (2020). Targeting multiple signaling pathways: The new approach to acute myeloid leukemia therapy. *Signal Transduction and Targeted Therapy, 5*(1), 288.

Chang, W., Wang, J., & Xiao, Y. (2020). Friedelin inhibits the growth and metastasis of human leukemia cells *via* modulation of MEK/ERK and PI3K/AKT signalling pathways. *Journal of B.U.ON., 25*(3), 1594–1599.

Chen, K. T. J., Gilabert-Oriol, R., Bally, M. B., & Leung, A. W. Y. (2019). Recent treatment advances and the role of nanotechnology, combination products, and immunotherapy in changing the therapeutic landscape of acute myeloid leukemia. *Pharmaceutical Research, 36*(9), 125.

Chen, L. C., Huang, H. L., HuangFu, W. C., Yen, S. C., Ngo, S. T., Wu, Y. W., Lin, T. E., Sung, T. Y., Lien, S. T., Tseng, H. J., Pan, S. L., Huang, W. J., & Hsu, K. C. (2020). Biological evaluation of selected flavonoids as inhibitors of MNKs targeting acute myeloid leukemia. *Journal of Natural Products, 83*(10), 2967–2975.

Chen, Y., Gan, D., Huang, Q., Luo, X., Lin, D., & Hu, J. (2018). Emodin and its combination with cytarabine induce apoptosis in resistant acute myeloid leukemia cells *in vitro* and *in vivo*. *Cellular Physiology and Biochemistry, 48*(5), 2061–2073.

Coulibaly, A., Haas, A., Steinmann, S., Jakobs, A., Schmidt, T. J., & Klempnauer, K. H. (2018). The natural anti-tumor compound Celastrol targets a Myb-C/EBPβ-p300 transcriptional module implicated in myeloid gene expression. *PLoS One, 13*(2), e0190934.

Crossnohere, N. L., Richardson, D. R., Reinhart, C., O'Donoghue, B., Love, S. M., Smith, B. D., & Bridges, J. F. P. (2019). Side effects from acute myeloid leukemia treatment: Results from a national survey. *Current Medical Research and Opinion, 35*(11), 1965–1970.

Dantas, B. B., Faheina-Martins, G. V., Coulidiati, T. H., Bomfim, C. C. B., da Silva Dias, C., Barbosa-Filho, J. M., & Araújo, D. A. M. (2015). Effects of curine in HL-60 leukemic cells: Cell cycle arrest and apoptosis induction. *Journal of Natural Medicines, 69*(2), 218–223.

Daver, N., Schlenk, R. F., Russell, N. H., & Levis, M. J. (2019). Targeting FLT3 mutations in AML: Review of current knowledge and evidence. *Leukemia, 33*(2), 299–312.

Dias, M. C., Pinto, D. C. G. A., & Silva, A. M. S. (2021). Plant flavonoids: Chemical characteristics and biological activity. *Molecules, 26*(17), 5377.

DiNardo, C. D., & Cortes, J. E. (2016). Mutations in AML: Prognostic and therapeutic implications. *Hematology American Society of Hematology Education Program, 2016*(1), 348–355.

DiNardo, C. D., Stein, E. M., de Botton, S., Roboz, G. J., Altman, J. K., Mims, A. S., Swords, R., Collins, R. H., Mannis, G. N., Pollyea, D. A., Donnellan, W., Fathi, A. T., Pigneux, A., Erba, H. P., Prince, G. T., Stein, A. S., Uy, G. L., Foran, J. M., Traer, E., ... Kantarjian, H. M. (2018). Durable remissions with ivosidenib in IDH1-mutated relapsed or refractory AML. *New England Journal of Medicine, 378*(25), 2386–2398.

Döhner, H., Estey, E., Grimwade, D., Amadori, S., Appelbaum, F. R., Büchner, T., Dombret, H., Ebert, B. L., Fenaux, P., Larson, R. A., Levine, R. L., Lo-Coco, F., Naoe, T., Niederwieser, D., Ossenkoppele, G. J., Sanz, M., Sierra, J., Tallman, M. S., Tien, H. F., ... Bloomfield, C. D. (2017). Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. *Blood, 129*(4), 424–447.

Döhner, H., Weisdorf, D. J., & Bloomfield, C. D. (2015). Acute myeloid leukemia. *New England Journal of Medicine, 373*(12), 1136–1152.

Dugan, J., Pollyea, D. A., Abbott, D., & Schultheiss, T. (2017). Bone marrow cellularity and recovery of blood counts after venetoclax and azacitidine in elderly acute myeloid leukemia patients unfit for induction chemotherapy. *Blood, 130*, 5086.

Ersöz, N. Ş., & Adan, A. (2022). Resveratrol triggers anti-proliferative and apoptotic effects in FLT3-ITD-positive acute myeloid leukemia cells *via* inhibiting ceramide catabolism enzymes. *Medical Oncology, 39*(3), 35.

Gu, R., Zhang, M., Meng, H., Xu, D., & Xie, Y. (2018). Gallic acid targets acute myeloid leukemia *via* Akt/mTOR-dependent mitochondrial respiration inhibition. *Biomedicine & Pharmacotherapy, 105*, 491–497.

Hasserjian, R. P., Campigotto, F., Klepeis, V., Fu, B., Wang, S. A., Bueso-Ramos, C., & Arber, D. A. (2014). De novo acute myeloid leukemia with 20–29% blasts is less aggressive than acute myeloid leukemia with ≥ 30% blasts in older adults: A B one M arrow Pathology Group study. *American journal of hematology, 89*(11), E193–E199.

Hou, H. A., & Tien, H. F. (2020). Genomic landscape in acute myeloid leukemia and its implications in risk classification and targeted therapies. *Journal of Biomedical Science, 27*(1), 81.

Hsiao, P. C., Hsieh, Y. H., Chow, J. M., Yang, S. F., Hsiao, M., Hua, K. T., Lin, C. H., Chen, H. Y., & Chien, M. H. (2013). Hispolon induces apoptosis through JNK1/2-mediated activation of a caspase-8, -9, and-3-dependent pathway in acute myeloid leukemia (AML) cells and inhibits AML xenograft tumor growth *in vivo*. *Journal of Agricultural and Food Chemistry, 61*(42), 10063–10073.

Hsiao, Y. C., Peng, S. F., Lai, K. C., Liao, C. L., Huang, Y. P., Lin, C. C., Lin, M. L., Liu, K. C., Tsai, C. C., Ma, Y. S., & Chung, J. G. (2019). Genistein induces apoptosis *in vitro* and has antitumor activity against human leukemia HL-60 cancer cell xenograft growth *in vivo*. *Environmental Toxicology, 34*(4), 443–456.

Huang, H., Chen, S., Van Doren, J., Li, D., Farichon, C., He, Y., Zhang, Q., Zhang, K., Conney, A. H., Goodin, S., Du, Z., & Zheng, X. (2015). α-Tomatine inhibits growth and induces apoptosis in HL-60 human myeloid leukemia cells. *Molecular Medicine Reports, 11*(6), 4573–4578.

Hui, H., Zhang, X., Li, H., Liu, X., Shen, L., Zhu, Y., Xu, J., Guo, Q., & Lu, N. (2016). Oroxylin A, a natural anticancer flavonoid compound, induces differentiation of t(8;21)-positive Kasumi-1 and primary acute myeloid leukemia cells. *Journal of Cancer Research and Clinical Oncology, 142*(7), 1449–1459.

Ilyas, A. M., Ahmad, S., Faheem, M., Naseer, M. I., Kumosani, T. A., Al-Qahtani, M. H., Gari, M., & Ahmed, F. (2015). Next generation sequencing of acute myeloid leukemia: Influencing prognosis. *BMC Genomics, 16*(Suppl 1), S5.

Issa, G. C., & DiNardo, C. D. (2021). Acute myeloid leukemia with IDH1 and IDH2 mutations: 2021 treatment algorithm. *Blood Cancer Journal, 11*(6), 107.

Iyer, S. G., Stanchina, M., Bradley, T. J., & Watts, J. (2022). Profile of glasdegib for the treatment of newly diagnosed acute myeloid leukemia (AML): Evidence to date. *Cancer Management and Research, 14*, 2267–2272.

Jafarbeigloo, H. R. G., Sheibani, S., & Bazmandeh, A. Z. (2021). Flavonoids kaempferol (KAE) and quercetine (QUE) inhibited proliferation of human leukemia THP-1 cells by up regulation of pro-apoptotic protein Bax and caspase 3/8 expression and down regulation of anti-apoptotic proteins Bcl-2, Bcl-xl and Mcl-1 expression. *Annals of Cancer Research and Therapy, 29*(1), 41–46.

Khalife, R., Stephany, E. H., Tarras, O., Hodroj, M. H., & Rizk, S. (2014). Antiproliferative and proapoptotic effects of topotecan in combination with thymoquinone on acute myelogenous leukemia. *Clinical Lymphoma Myeloma and Leukemia, 14*, S46–S55.

Khoury, J. D., Solary, E., Abla, O., Akkari, Y., Alaggio, R., Apperley, J. F., Bejar, R., Berti, E., Busque, L., Chan, J. K. C., Chen, W., Chen, X., Chng, W. J., Choi, J. K., Colmenero, I., Coupland, S. E., Cross, N. C. P., De Jong, D., Elghetany, M. T., ... Hochhaus, A. (2022). The 5th edition of the World Health Organization classification of haematolymphoid tumours: Myeloid and histiocytic/dendritic neoplasms. *Leukemia, 36*(7), 1703–1719.

Kim, S. H., Lee, I. C., Baek, H. S., Shin, I. S., Moon, C., Bae, C. S., Kim, S. H., Kim, J. C., & Kim, H. C. (2014). Mechanism for the protective effect of diallyl disulfide against cyclophosphamide acute urotoxicity in rats. *Food and Chemical Toxicology, 64*, 110–118.

Kopustinskiene, D. M., Jakstas, V., Savickas, A., & Bernatoniene, J. (2020). Flavonoids as anticancer agents. *Nutrients, 12*(2), 457.

Labbozzetta, M., Poma, P., & Notarbartolo, M. (2023). Natural inhibitors of *P*-glycoprotein in acute myeloid leukemia. *International Journal of Molecular Sciences, 24*(4), 4140.

Lee, W. J., Hsiao, M., Chang, J. L., Yang, S. F., Tseng, T. H., Cheng, C. W., Chow, J. M., Lin, K. H., Lin, Y. W., Liu, C. C., Lee, L. M., & Chien, M. H. (2015). Quercetin induces mitochondrial-derived apoptosis *via* reactive oxygen species-mediated ERK activation in HL-60 leukemia cells and xenograft. *Archives of Toxicology, 89*(7), 1103–1117.

Li, Z. R., Suo, F. Z., Guo, Y. J., Cheng, H. F., Niu, S. H., Shen, D. D., Zhao, L. J., Liu, Z. Z., Maa, M., Yu, B., Zheng, Y. C., & Liu, H. M. (2020). Natural protoberberine alkaloids, identified as potent selective LSD1 inhibitors, induce AML cell differentiation. *Bioorganic Chemistry, 97*, 103648.

Li, Z. Y., Huang, W. C., Tu, R. S., Gu, P. Y., Lin, C. F., & Liou, C. J. (2016). Sophoraflavanone G induces apoptosis in human leukemia cells and blocks MAPK activation. *The American Journal of Chinese Medicine, 44*(1), 165–176.

Liu, T., Men, Q., Wu, G., Yu, C., Huang, Z., Liu, X., & Li, W. (2015). Tetrandrine induces autophagy and differentiation by activating ROS and Notch1 signaling in leukemia cells. *Oncotarget, 6*(10), 7992–8006.

Long, H., Hou, Y., Li, J., Song, C., & Ge, Z. (2023). Azacitidine is synergistically lethal with XPO1 inhibitor selinexor in acute myeloid leukemia by targeting XPO1/eIF4E/c-MYC signaling. *International Journal of Molecular Sciences, 24*(7), 6816.

Mahbub, A. A., Le Maitre, C. L., Haywood-Small, S., McDougall, G., Cross, N., & Jordan-Mahy, N. (2013). Differential effects of polyphenols on proliferation and apoptosis in human myeloid and lymphoid leukemia cell lines. *Anti-Cancer Agents in Medicinal Chemistry, 13*, 1601–1613.

Maioral, M. F., Stefanes, N. M., Bigolin, Á., Zatelli, G. A., Philippus, A. C., de Barcellos Falkenberg, M., & Santos-Silva, M. C. (2019). MICONIDINE acetate, a new selective and cytotoxic compound with synergic potential, induces cell cycle arrest and apoptosis in leukemia cells. *Investigational New Drugs, 37*(5), 912–922.

Mesbahi, Y., Trahair, T. N., Lock, R. B., & Connerty, P. (2022). Exploring the metabolic landscape of AML: From haematopoietic stem cells to myeloblasts and leukaemic stem cells. *Frontiers in Oncology, 12*, 807266.

Miękus, N., Marszałek, K., Podlacha, M., Iqbal, A., Puchalski, C., & Świergiel, A. H. (2020). Health benefits of plant-derived sulfur compounds, glucosinolates, and organosulfur compounds. *Molecules, 25*(17), 3804.

Momekov, G., Yossifov, D., Guenova, M., Michova, A., Stoyanov, N., Konstantinov, S., Ionkov, T., Sacheva, P., & Ionkova, I. (2014). Apoptotic mechanisms of the biotechnologically produced arylnaphtalene lignan justicidin B in the acute myeloid leukemia-derived cell line HL-60. *Pharmacological Reports, 66*(6), 1073–1076.

Mondal, A., Gandhi, A., Fimognari, C., Atanasov, A. G., & Bishayee, A. (2019). Alkaloids for cancer prevention and therapy: Current progress and future perspectives. *European Journal of Pharmacology, 858*, 172472.

Murata, T., Kohno, S., Ogawa, K., Ito, C., Itoigawa, M., Ito, M., Hikita, K., & Kaneda, N. (2020). Cytotoxic activity of dimeric acridone alkaloids derived from *Citrus* plants towards human leukaemia HL-60 cells. *Journal of Pharmacy and Pharmacology, 72*(10), 1445–1457.

Ordóñez, P. E., Sharma, K. K., Bystrom, L. M., Alas, M. A., Enriquez, R. G., Malagón, O., Jones, D. E., Guzman, M. L., & Compadre, C. M. (2016). Dehydroleucodine, a sesquiterpene lactone from *Gynoxys Verrucosa*, demonstrates cytotoxic activity against human leukemia cells. *Journal of Natural Products, 79*(4), 691–696.

Perveen, S., & Al-Taweel, A. (Eds.). (2018). *Terpenes and terpenoids* (1st ed.). BoD–Books on Demand.

Ramos, N. R., Mo, C. C., Karp, J. E., & Hourigan, C. S. (2015). Current approaches in the treatment of relapsed and refractory acute myeloid leukemia. *Journal of Clinical Medicine, 4*(4), 665–695.

Rodrigues, A. C. B. D. C., Costa, R. G. A., Silva, S. L. R., Dias, I. R. S. B., Dias, R. B., & Bezerra, D. P. (2021). Cell signaling pathways as molecular targets to eliminate AML stem cells. *Critical Reviews in Oncology/Hematology, 160*, 103277.

Roma, A., Rota, S. G., & Spagnuolo, P. A. (2018). Diosmetin induces apoptosis of acute myeloid leukemia cells. *Molecular Pharmaceutics, 15*(3), 1353–1360.

Salucci, S., Burattini, S., Buontempo, F., Orsini, E., Furiassi, L., Mari, M., Lucarini, S., Martelli, A. M., & Falcieri, E. (2018). Marine bisindole alkaloid: A potential apoptotic inducer in human cancer cells. *European Journal of Histochemistry, 62*(2), 2881.

Sarkar, M. K., Mahapatra, S. K., & Vadivel, V. (2020). Oxidative stress mediated cytotoxicity in leukemia cells induced by active *Phyto*-constituents isolated from traditional herbal drugs of West Bengal. *Journal of Ethnopharmacology, 251*, 112527.

Shao, R. G., & Zhen, Y. S. (2012). Research and development of highly potent antibody-based drug conjugates and fusion proteins for cancer therapy. *Recent Advances in Cancer Research and Therapy*. Elsevier, Pp. 153–171.

Shimony, S., Canaani, J., Kugler, E., Nachmias, B., Ram, R., Henig, I., Frisch, A., Ganzel, C., Vainstein, V., Moshe, Y., Aumann, S., Yeshurun, M., Ofran, Y., Raanani, P., & Wolach, O. (2022). Gilteritinib monotherapy for relapsed/refractory FLT3 mutated acute myeloid leukemia: A real-world, multi-center, matched analysis. *Annals of Hematology, 101*(9), 2001–2010.

Spirin, P., Shyrokova, E., Lebedev, T., Vagapova, E., Smirnova, P., Kantemirov, A., Dyshlovoy, S. A., Amsberg, G. V., Zhidkov, M., & Prassolov, V. (2021). Cytotoxic marine alkaloid 3, 10-dibromofascaplysin induces apoptosis and synergizes with cytarabine resulting in leukemia cell death. *Marine Drugs, 19*(9), 489.

Su, L., Shi, Y. Y., Liu, Z. Y., & Gao, S. J. (2022). Acute myeloid leukemia with *CEBPA* mutations: Current progress and future directions. *Frontiers in Oncology, 12*, 806137.

Tan, M., Zhang, Q., Yuan, X., Chen, Y., & Wu, Y. (2019). Synergistic killing effects of homoharringtonine and arsenic trioxide on acute myeloid leukemia stem cells and the underlying mechanisms. *Journal of Experimental & Clinical Cancer Research, 38*(1), 308.

Thao, N. P., Luyen, B. T. T., Kim, E. J., Kang, H. K., Kim, S., Cuong, N. X., Nam, N. H., Kiem, P. V., Minh, C. V., & Kim, Y. H. (2014). Asterosaponins from the Starfish *Astropecten monacanthus* suppress growth and induce apoptosis in HL-60, PC-3, and SNU-C5 human cancer cell lines. *Biological & Pharmaceutical Bulletin, 37*(2), 315–321.

Thuy, T. T., Tam, N. T., Anh, N. T. H., Hau, D. V., Phong, D. T., Thang, L. Q., Adorisio, S., Sung, T. V., & Delfino, D. V. (2017). 20-Hydroxyecdysone from *Dacrycarpus imbricatus* bark inhibits the proliferation of acute myeloid leukemia cells. *Asian Pacific Journal of Tropical Medicine, 10*(2), 157–159.

Tiong, I. S., & Wei, A. H. (2019). New drugs creating new challenges in acute myeloid leukemia. *Genes, Chromosomes & Cancer, 58*(12), 903–914.

Vieira Torquato, H. F., Ribeiro-Filho, A. C., Buri, M. V., Araújo, R. T., Jr, Pimenta, R., de Oliveira, J. S. R., Filho, V. C., Macho, A., Paredes-Gamero, E. J., & de Oliveira Martins, D. T. (2017). Canthin-6-one induces cell death, cell cycle arrest and differentiation in human myeloid leukemia cells. *Biochimica et Biophysica Acta (BBA) - General Subjects, 1861*(4), 958–967.

Wachter, F., & Pikman, Y. (2024). Pathophysiology of acute myeloid leukemia. *Acta Haematologica, 147*(2), 229–246.

Wang, E. S. (2014). Treating acute myeloid leukemia in older adults. *Hematology American Society of Hematology Education Program, 2014*(1), 14–20.

Wang, E. S., & Baron, J. (2020). Management of toxicities associated with targeted therapies for acute myeloid leukemia: When to push through and when to stop. *Hematology American Society of Hematology Education Program, 2020*(1), 57–66.

Wang, F., Chen, L., Zhu, S., Wang, S., Chen, C., Zhang, W., Wang, X., Zhang, J., & Wang, M. (2018). Sulforaphane induces apoptosis of acute human leukemia cells through modulation of bax, bcl-2 and caspase-3. *International Journal of Pharmacology, 14*(3), 369–376.

Wang, W., Sun, C., Mao, L., Ma, P., Liu, F., Yang, J., & Gao, Y. (2016a). The biological activities, chemical stability, metabolism and delivery systems of quercetin: A review. *Trends in Food Science & Technology, 56*, 21–38.

Wang, X. D., Li, C. Y., Jiang, M. M., Li, D., Wen, P., Song, X., ... He, Z. D. (2016b). Induction of apoptosis in human leukemia cells through an intrinsic pathway by cathachunine, a unique alkaloid isolated from *Catharanthus roseus*. *Phytomedicine, 23*(6), 641–653.

Wei, A. H., & Tiong, I. S. (2017). Midostaurin, enasidenib, CPX-351, gemtuzumab ozogamicin, and venetoclax bring new hope to AML. *Blood, 130*(23), 2469–2474.

Wen, C., Lu, X., Sun, Y., Li, Q., Liao, J., & Li, L. (2023). Naringenin induces the cell apoptosis of acute myeloid leukemia cells by regulating the lncRNA XIST/miR-34a/HDAC1 signaling. *Heliyon, 9*(5) e15826.

Westphal, S., McGeary, A., Rudloff, S., Wilke, A., & Penack, O. (2017). The green tea catechin epigallocatechin gallate ameliorates graft-versus-host disease. *PLoS One, 12*(1), e0169630.

Wu, P. S., Wang, C. Y., Hsu, H. J., Yen, J. H., & Wu, M. J. (2023). 8-hydroxydaidzein induces apoptosis and inhibits AML-associated gene expression in U-937 cells: Potential phytochemical for AML treatment. *Biomolecules, 13*(11), 1575.

Wu, S. S., Chen, L. G., Lin, R. J., Lin, S. Y., Lo, Y. E., & Liang, Y. C. (2013). Cytotoxicity of (-)-vitis in B in human leukemia cells. *Drug and Chemical Toxicology, 36*(3), 313–319.

Xiao, Y., Deng, T., & Wang, D. (2020). Davanone terpenoid inhibits cisplatin-resistant acute myeloid leukemia cancer cell growth by inducing caspase-dependent apoptosis, loss of mitochondrial membrane potential, inhibition of cell migration and invasion and targeting PI3K/AKT/MAPK signalling pathway. *Journal of B. U. ON., 25*(3), 1607–1613.

Xiong, X. X., Liu, J. M., Qiu, X. Y., Pan, F., Yu, S. B., & Chen, X. Q. (2015). Piperlongumine induces apoptotic and autophagic death of the primary myeloid leukemia cells from patients *via* activation of ROS-p38/JNK pathways. *Acta Pharmacologica Sinica, 36*(3), 362–374.

Xu, H. H., Chang, X., Luo, Q., & Zhang, B. (2023). Effect of alkannin on apoptosis of acute myeloid leukemia cells by down-regulating Trx/Akt pathway. *Chinese Traditional and Herb Drugs, 54*(4), 1138–1148.

Yang, Y. B., Han, Z. Z., Tian, T., Liao, Q., Geng, J. R., & Xiao, Y. (2023). Chemical constituents from aerial parts of *Scoparia dulcis*. *Chinese Herbal Medicines, 15*(1), 151–154.

Zarka, J., Short, N. J., Kanagal-Shamanna, R., & Issa, G. C. (2020). Nucleophosmin 1 mutations in acute myeloid leukemia. *Genes, 11*(6), 649.

Zeidner, J. F., & Karp, J. E. (2015). Clinical activity of alvocidib (flavopiridol) in acute myeloid leukemia. *Leukemia Research, 39*(12), 1312–1318.

Zhang, H., Li, L., Li, M., Huang, X., Xie, W., Xiang, W., & Yao, P. (2017a). Combination of betulinic acid and chidamide inhibits acute myeloid leukemia by suppression of the HIF1α pathway and generation of reactive oxygen species. *Oncotarget, 8*(55), 94743–94758.

Zhou, C. X., Yu, Y. E., Sheng, R., Mo, J. X., Huang, M., Ouyang, L., & Gan, L. S. (2017). Cimicifoetones A and B, dimeric prenylindole alkaloids as black pigments of *Cimicifuga* foetida. *Chemistry, an Asian Journal, 12*(12), 1277–1281.

Zhang, Y., Wang, L., Zi, Y., Zhang, L., Guo, Y., & Huang, Y. (2017b). Oridonin effectively reverses the drug resistance of cisplatin involving induction of cell apoptosis and inhibition of MMP expression in human acute myeloid leukemia cells. *Saudi Journal of Biological Sciences, 24*(3), 678–686.

Zhou, C., Martinez, E., Di Marcantonio, D., Solanki-Patel, N., Aghayev, T., Peri, S., Ferraro, F., Skorski, T., Scholl, C., Fröhling, S., Balachandran, S., Wiest, D. L., & Sykes, S. M. (2017). JUN is a key transcriptional regulator of the unfolded protein response in acute myeloid leukemia. *Leukemia, 31*(5), 1196–1205.

Zhou, H., Ning, Y., Zeng, G., Zhou, C., & Ding, X. (2021). Curcumin promotes cell cycle arrest and apoptosis of acute myeloid leukemia cells by inactivating AKT. *Oncology Reports, 45*(4), 11.