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Emerging drugs targeting cellular redox homeostasis to eliminate acute myeloid leukemia stem cells

Rafaela G.A. Costa [a], Suellen L.R. Silva [a], Ingrid R.S.B. Dias [a], Maiara de S. Oliveira [a], Ana Carolina B. da C. Rodrigues [a], Rosane B. Dias [a,b], Daniel P. Bezerra [a,*]

[a] Gonçalo Moniz Institute, Oswaldo Cruz Foundation (IGM-FIOCRUZ/BA), Salvador, Bahia, 40296-710, Brazil
[b] Department of Propedeutics, School of Dentistry of the Federal University of Bahia, Salvador, Bahia, 40110-909, Brazil

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ABSTRACT

Acute myeloid leukemia (AML) is a very heterogeneous group of disorders with large differences in the percentage of immature blasts that presently are classified according to the specific mutations that trigger malignant proliferation among thousands of mutations reported thus far. It is an aggressive disease for which few targeted therapies are available and still has a high recurrence rate and low overall survival. The main reason for AML relapse is believed to be due to leukemic stem cells (LSCs) that have unlimited self-renewal capacity and long residence in a quiescent state, which promote greater resistance to traditional therapies for this cancer. AML LSCs have low oxidative stress levels, which appear to be caused by a combination of low mitochondrial activity and high activity of ROS-removing pathways. In this sense, oxidative stress has been thought to be an important new potential target for the treatment of AML patients, targeting the eradication of AML LSCs. The aim of this review is to discuss some drugs that induce oxidative stress to direct new goals for future research focusing on redox imbalance as an effective strategy to eliminate AML LSCs.

1. Introduction

Acute myeloid leukemia (AML) is a very heterogeneous group of disorders with large differences in the percentage of immature blasts that presently are classified according to the specific mutations that trigger malignant proliferation among thousands of mutations reported thus far [1–5]. The American Cancer Society estimated 20,380 new cases of AML and 11,310 deaths in the United States for 2023 [6].

According to the French-American-British (FAB) classification, AML can be subclassified into undifferentiated acute myeloblastic leukemia, acute myeloblastic leukemia with minimal maturation, acute myeloblastic leukemia with maturation, acute promyelocytic leukemia, acute myelomonocytic leukemia, acute myelomonocytic leukemia with eosinophilia, acute monocytic leukemia, acute erythroid leukemia and acute megakaryoblastic leukemia [7–10].

In the most recent update of the World Health Organization (WHO) AML classification, there is a separation of AML with defining genetic abnormalities from AML defined by differentiation. AML with defining genetic abnormalities includes acute promyelocytic leukemia with *PML::RARA* fusion; AML with *RUNX1::RUNX1T1* fusion; AML with *CBFB::MYH11* fusion; AML with *DEK::NUP214* fusion; AML with *RBM15::MRTFA* fusion; AML with *BCR::ABL1* fusion; AML with *KMT2A* rearrangement; AML with *MECOM* rearrangement; AML with *NUP98* rearrangement; AML with *NPM1* mutation; AML with *CEBPA* mutation; AML myelodysplasia-related; and AML with other defined genetic alterations. AML defined by differentiation includes AML with minimal differentiation, AML without maturation, AML with maturation, acute basophilic leukemia, acute myelomonocytic leukemia, acute monocytic leukemia, acute erythroid leukemia, and acute megakaryoblastic leukemia [11].

AML can affect individuals of any age; although it is the most common malignancy in children aged 15 years or younger, it becomes more common with aging. Generally, adults correspond to the group of individuals who are most affected by this type of neoplasm, which reduces the success of therapeutic alternatives due to age. Thus, the disease has a poor prognosis when compared to younger individuals affected by AML [4,12–14].

AML is an aggressive disease for which few targeted therapies are available. The standard protocol for treatment has remained almost unchanged for more than four decades and basically consists of the

* Corresponding author.
E-mail address: daniel.bezerra@fiocruz.br (D.P. Bezerra).

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administration of cytarabine (100 mg/m^2/day by continuous infusion for 7 days) combined with anthracycline (daunorubicin 60 mg/m^2/day or idarubicin 12 mg/m^2/day for 3 days), where blasts can often be eliminated, thus achieving remission [15].

Usually, the patient undergoes induction therapy with the aim of achieving complete remission, and all of the leukemic cells must be destroyed. Although most patients are successful in remission, in many cases, minimal residual disease (MRD) remains, consequently increasing the rate of disease relapse. In this context, AML currently still has a high recurrence rate and low overall survival [16–19]. The main reason for AML relapse is believed to be due to a subpopulation of leukemia cells called leukemia stem cells (LSCs) or leukemia initiating cells (LICs) [3,20–24].

AML LSCs are a rare blast immature population that are normally in a quiescent state and can become active as they have unlimited self-renewal capacity that continuously propagates leukemic cell clones and a large number of mature AML blast cells. Due to their unlimited self-renewal capacity, these cells are characterized by their high repopulation potential and long residence in a quiescent state of the G_0 phase, playing a key role in AML relapse and refractoriness [3,24–27].

AML LSCs have very similar characteristics to normal hematopoietic stem cells (HSCs). The cell cycle quiescence and the high capacity for self-renewal make it possible to use similar molecular mechanisms for their self-renewal and maintenance of an undifferentiated state that allows their differentiation into more developed progenitor cells. Both AML LSCs and HSCs express a $CD34^+CD38^-$ phenotype [23,28–32]. In addition, other markers, including CD123 [33], CD96 [34], CLL-1 [35], TIM-3 [36], CD93 [37], and CD99 [38], have also been found to be expressed in AML LSCs.

Studies have shown that high levels of oxidative stress are found in AML, which seems to affect the proliferation, differentiation and self-renewal capacity of HSCs, consequently impairing cell growth. This can be explained by the fact that oxidative stress causes a redox imbalance, which induces cell damage [39,40]. Under normal conditions, controlled levels of oxidative stress play an important role in the self-renewal, regeneration and proliferation of HSCs. On the other hand, elevated levels of oxidative stress induce fatal oxidative damage to DNA and cellular proteins, thus contributing to the differentiation of leukemic blasts and favoring the development of AML [41,42].

Interestingly, AML LSCs have low oxidative stress levels, which appear to be caused by a combination of low mitochondrial activity and high activity of ROS-removing pathways. LSCs are highly dependent on mitochondrial regulatory mechanisms and are sensitive to oxidative stress as a result of their low activity [42,43]. In this sense, oxidative stress is thought of as an important new potential target for the treatment of AML, including AML LSCs. The aim of this review is to discuss some drugs that induce oxidative stress and are able to eliminate AML LSCs to direct new goals for future research. Searches were carried out in the scientific database PubMed comprising all papers in English published until November 2022.

1.1. Cellular redox homeostasis

Aerobic organisms use oxygen for cellular respiration, but this process produces free radicals, which are molecular fragments that can exist independently and attempt to bond with other molecules, atoms, or even individual electrons to form a stable compound. The transfer of one or more electrons from a donor to an acceptor is referred to as an oxidative process [44–47].

Cellular redox homeostasis is maintained by the balance between oxidizing agents and the cellular antioxidant defense system. These oxidizing agents are reactive species, which include reactive oxygen species (ROS), reactive nitrogen species (RNS), and less commonly reactive sulfur species (RSS), and their excess in cells is known as oxidative stress [47–52]. These reactive species can be free radicals or nonfree radical compounds (Table 1). In living organisms, nonfree radical species easily initiate free radical reactions, and oxidative stress is usually caused by excess ROS [47]. Most biological processes are regulated by redox interactions, which play an important role in the regulation of cell signaling, development, health and pathologies [53].

Table 1
Examples of ROS, RNS and RSS of biological interest.

Free radical		Nonfree radical	
Name	Symbol	Name	Symbol
ROS			
Oxygen (biradical)	$O_2^{\bullet\bullet}$	Hydrogen peroxide	H_2O_2
Superoxide ion	$O_2^{\bullet-}$	Ozone	O_3
Hydroxyl	$^{\bullet}OH$	Singlet oxygen	$^1O_2$
Hydroperoxyl	$HO_2^{\bullet}$	Hypobromous acid	HOBr
Carbonate	$CO_3^{\bullet-}$	Hypochlorous acid	HOCl
Peroxyl	$ROO^{\bullet}$	Hypoiodous acid	HOI
Alkoxyl	$RO^{\bullet}$	Organic peroxides	ROOH
Carbon dioxide radical	$CO_2^{\bullet-}$	Peroxynitrite	$ONOO^-$
		Peroxynitrate	O_2NOO^-
		Peroxynitrous acid	ONOOH
		Peroxomono-carbonate	$HOOCO_2^-$
		Carbon monoxide	CO
RNS			
Nitric oxide	$NO^{\bullet}$	Nitrosyl cation	NO^+
Nitrogen dioxide	$NO_2^{\bullet}$	Nitrous acid	HNO_2
Nitrate radical	$NO_3^{\bullet}$	Nitroxyl anion	NO^-
		Dinitrogen trioxide	N_2O_3
		Dinitrogen tetroxide	N_2O_4
		Dinitrogen pentoxide	N_2O_5
		Alkyl peroxynitrites	ROONO
		Alkyl peroxynitrates	RO_2ONO
		Nitryl chloride	NO_2Cl
		Peroxyacetyl nitrate	$CH_3C(O)OONO_2$
RSS			
Thiyl radical S$^{\bullet}$	$RS^{\bullet}$	Hydrogen sulfide	H_2S
		Disulfide	RSSR
		Disulfide-S-monoxide	RS(O)SR
		Disulfide-S-dioxide	$RS(O)_2SR$
		Sulfenic acid	RSOH
		Thiol/sulfide	RSR

Oxidizing compounds can come from endogenous and exogenous sources. In mammals, the primary source of ROS is mitochondrial energy production during ATP production by the mitochondrial oxidative phosphorylation system (OXPHOS). ROS are produced by reactions in the electron transport chain (ETC) [42,47,54–56]. Exogenous sources of oxidizing compounds include radiation, chemical reagents, certain foods and environmental pollutants, and drugs and their metabolites [47,57].

Free radicals can affect all cellular macromolecules and cause cell and tissue damage. As a result, these radicals may cause damage and activate redox signaling pathways, and excess free radicals can lead to cell death. Under physiological conditions, the effects of these compounds are seen only locally where they are produced [57–60].

Antioxidants inhibit oxidation and counteract oxidative stress. These antioxidants can be endogenous or exogenous [61]. Endogenous antioxidants can be enzymatic or nonenzymatic. Enzymatic antioxidants include superoxide dismutases (SODs), superoxide reductases (SORs), catalase, glutathione peroxidase (GPx), glutathione reductase (GRx), glutathione-S-transferase (GST), thioredoxin reductase (TrxR) and peroxiredoxins (PRXs). Lipoic acid, glutathione, thioredoxin and L-arginine are considered nonenzymatic. On the other hand, some antioxidant nutrients cannot be produced by the body and must be obtained exogenously through foods [47,58,62–65].

The summarized mechanism by which these molecules carry out their antioxidant action is shown in Fig. 1. Interestingly, antioxidant enzymes that control ROS homeostasis are altered in several diseases, including cancer [66].

SODs convert peroxide into hydrogen peroxide and oxygen. There are five types of SODs that differ by the ion in their catalytic site, including Fe, Mn, Ni, Cu or Cu and Zn [67]. In mammals, the main SOD family is SOD1, with Cu and Zn in the cytoplasm. SOD2 with Mn is in the

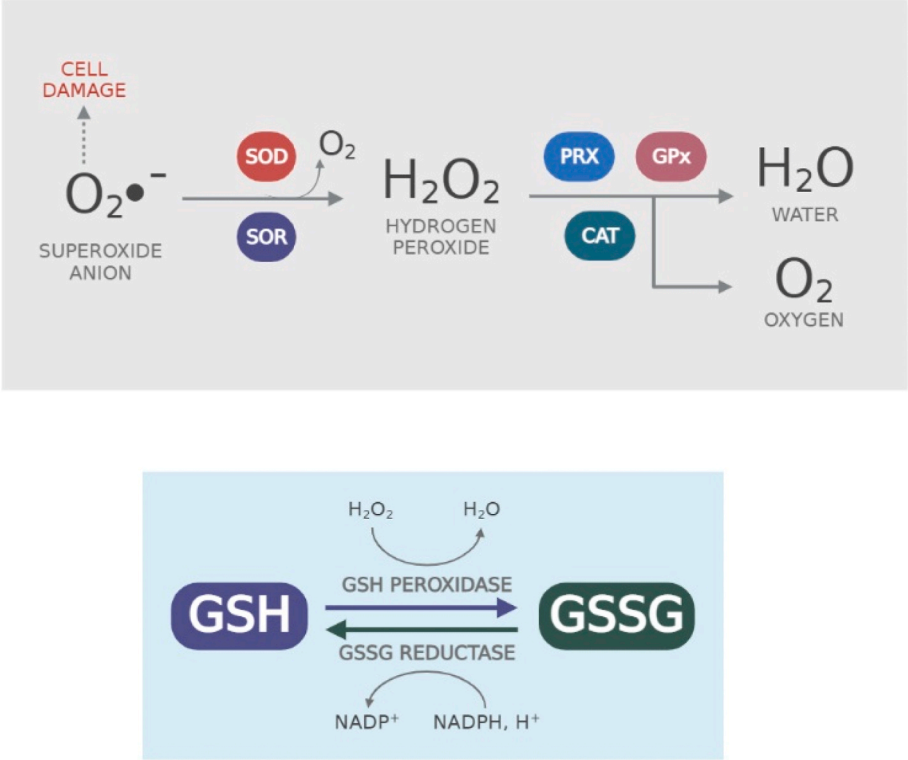

Fig. 1. Conversion of superoxide to water and oxygen. The enzyme superoxide dismutase converts superoxide to hydrogen peroxide. It can be detoxified to water and oxygen using catalase or glutathione peroxidase (GSH, reduced glutathione; GSSG, oxidized glutathione). Hydrogen peroxide spontaneously degrades to the reactive hydroxyl radical ($^{\bullet}OH$).

mitochondrial matrix, and both have tumor suppressor activity [68]. SOD2 protects cells against oxidative stress, and its loss leads to defective hematopoiesis [69,70]. Polymorphisms in SODs lead to high levels of ROS, which may contribute to the malignant transformation of cells [71].

SORs reduce superoxide and are found in various organisms. They have a unique iron ion catalytic site and need electron donors to regenerate. They are classified by metallic centers and extra domains [67,72,73]. Aside from their antioxidant activity in reducing ROS, little is known about the role of SORs in leukemia and LSCs.

Catalase enzymes convert H_2O_2 into O_2 and H_2O. They can be classified into three types based on structure and function, for example, typical catalases, peroxidase catalases and manganese catalases. Human catalase is a typical catalase with an iron protoporphyrin IX active center and NADPH cofactor [74–76]. CATs are crucial in protecting cells against oxidative stress and are found in peroxisomes in normal cells. In cancer cells, they can impede apoptosis. CAT's role in tumors is complex and can act as both a survival enhancer and tumor suppressor. Studies show that elevated catalase expression in AML is associated with a positive therapy response, and genetic polymorphisms can alter catalase expression and susceptibility to oxidative damage [66,71,75,76].

Glutathione is known as the most abundant antioxidant in the cell [77]. Glutathiones exist in oxidized and reduced forms: glutathione in its oxidized (GSSG) and reduced (GSH) states. GST is an enzyme that helps detoxify by conjugating GSH to xenobiotics. It helps metabolize and detoxify various harmful substances and protect tissues against oxidative damage [78–80].

GRx is a GST helper enzyme; together, GST and GRx use NADPH to regenerate GSH from GSSG (also known as the glutathione antioxidant system). Thus, glutathione functions as a direct scavenger of ROS, and polymorphisms in the GST gene have been related to failures in enzymatic activity, implying greater susceptibility to leukemia [70,71].

The maintenance of redox homeostasis can be guaranteed by the stability of GSH/GSSG, which enables normal biological processes; on the other hand, the accumulation of GSSG/GSH under abnormal conditions can result in cell death mediated by oxidative stress [56].

GPXs have selenocysteine in their active sites and four isoforms: GPX1-4. GPX1 is the most abundant and codes for mitochondrial peroxide glutathione. GPX1 gene polymorphism can decrease enzyme activity and increase cancer risk in Caucasians [71,81]. GPX4 has been shown to be an important enzyme in the detoxification of lipid hydroperoxides [70].

TrxR is part of the thioredoxin antioxidant system, which includes NADPH, TrxR, thioredoxin and TXNIP. TXNIP inhibits thioredoxin activity by binding to it. TrxR is a selenoenzyme that uses NADPH to keep thioredoxin reduced [82–84]. Mammals have three TrxR isoforms with different locations and expression levels: TrxR 1 in the cytoplasm, TrxR 2 in mitochondria and TrxR 3 in testis. Two thioredoxin isoforms (Trx1 and Trx2) are also found in the cytoplasm and mitochondria [82–84]. In particular, overexpression of thioredoxin 1 enhanced the antitumor function of T cells [85].

PRXs are a family of six small antioxidant proteins with essential cysteine residues that scavenge cellular ROS. Cysteine residues can be oxidized and generate intermolecular disulfides with nearby proteins, which are reduced by thioredoxin. PRXs I-IV have sequences for CDK phosphorylation and may regulate the cell cycle [70,86–88]. PRX I is produced during serum stimulation and oxidative stress. Its loss can cause hemolytic anemia and increased malignancies. PRX II loss causes hemolytic anemia compensated by increased erythroid progenitor activity. PRX III is mitochondrial-specific and converts hydrogen peroxide to water. Its deficiency causes ROS accumulation and may regulate mitochondria-mediated apoptosis [70,88–90].

1.2. *Pleiotropic effect of oxidative stress in AML*

Oxidative stress has both tumor-promoting and tumor-suppressing

functions [65]. Furthermore, the physiological level of ROS is important for the self-renewal, differentiation and proliferation of HSCs [42,91,92].

HSCs reside in bone marrow in low-oxygen environments known as stem cell niches. These hypoxic conditions cause metabolic changes such as low mitochondrial activity and low membrane potential [93–96]. Quiescent HSCs primarily generate energy through anaerobic glycolysis, which reduces the burden of ROS-mediated oxidative stress [42,97].

Moreover, HSCs also use the cellular antioxidant system, including antioxidant molecules (e.g., glutathione, thioredoxin, NADPH) and antioxidant enzymes (e.g., catalase, SOD, glutathione peroxidase). Other ROS regulatory mechanisms used by HSCs include the interactions of cells with their microenvironment [98] and mitophagy [99], a subtype of autophagy where selective degradation of mitochondria occurs, which controls mitochondrial quantity and quality.

On the other hand, an increase in ROS (moderate level of ROS) is critical during HSC differentiation, which occurs with an increase in mitochondrial activity through OXPHOS [42,92,93]. Therefore, HSCs can self-renew (when ROS levels are reduced) or differentiate (when ROS levels are moderate/higher) depending on the ROS level [100,101].

Nevertheless, HSCs are susceptible to ROS accumulation [70]. Thus, when there is a high concentration of ROS, there can be damage to cell functions and structures that can result in cell death or abnormal hematopoiesis, with malignant transformation to LSCs being a crucial event for the progression of hematological malignancies such as AML and its aggressiveness [40,102]. Studies suggest that ROS accumulation actively participates in the conversion of normal HSCs into leukemic cells [70,103].

Interestingly, the amount of intracellular ROS also differs in AML cell subpopulations, where bulk AML cells have a high level of ROS and AML LSCs, such as HSCs, have a low level of ROS [42,104]. AML blasts present high levels of oxygen-derived radicals and thus greater endogenous oxidative stress than normal leukocytes. The antioxidant system in these cells is normally deficient, so high and persistent levels of ROS produce DNA damage leading to mutagenesis [40,71].

In AML cells, the main form of ROS is the superoxide anion ($O_2^{\bullet-}$) [40]. In primary human AML cells, where the intrinsic property is the altered metabolism of glutathione, it is possible to observe oxidative stress that contributes to leukemogenesis [105]. Reduced catalase expression may also be responsible for H_2O_2 accumulation in leukemic cells [69]. Furthermore, constitutive activation of NADPH oxidase 2 (NOX2) has been shown to favor overproduction of ROS and is present in more than 60% of AML patients [106].

On the other hand, AML LSCs that are characterized by low ROS levels exhibit low cellular oxidative status and aberrantly overexpress the BCL-2 gene. In this respect, BCL-2 inhibition is able to reduce OXPHOS, thus selectively eradicating quiescent LSCs [107]. Thus, in AML, a low level of ROS is related to LSC quiescence, while a high level favors blast proliferation [108,109]. Fig. 2 shows the behavior of LSCs against different levels of ROS.

In addition to promoting leukemogenesis in AML, ROS can promote chemotherapy resistance. An example is arsenic trioxide, an antileukemic drug used for the treatment of AML. Although it is commonly used, many patients have high therapeutic resistance because some signaling pathways, such as JAK2/STAT3, reduce the antileukemic activity of arsenic trioxide, reducing the amount of ROS and protecting the cell from apoptosis. Based on this, a study demonstrated that the use of potent inhibitors of the JAK2/STAT3 pathway is an alternative to increase the sensitivity of AML cells to combined treatment with arsenic trioxide by increasing ROS and DNA damage. In this work, the authors demonstrated that the increase in ROS increased the rate of apoptosis in AML cells treated with the combination of arsenic trioxide and ruxolitinib, thus revealing that the antileukemic effect of arsenic trioxide is mediated by the elevation of ROS and DNA damage [110].

Regarding the tumor-suppressing properties of oxidative stress, elevated oxidative damage and enhanced ROS-dependent death signaling can also successfully stop some stages of tumorigenesis and make tumor cells more susceptible to cell death [65,111]. Increased oxidative stress associated with cancer progression causes metabolic reprogramming of cells, allowing them to tolerate the negative effects of increased ROS [112,113]. As a result, tumor cells become more dependent on the cellular antioxidant system. Furthermore, ROS accumulation can lead to senescence and various forms of cell death, especially ferroptosis, which is caused by iron-dependent lipid peroxidation [114–116].

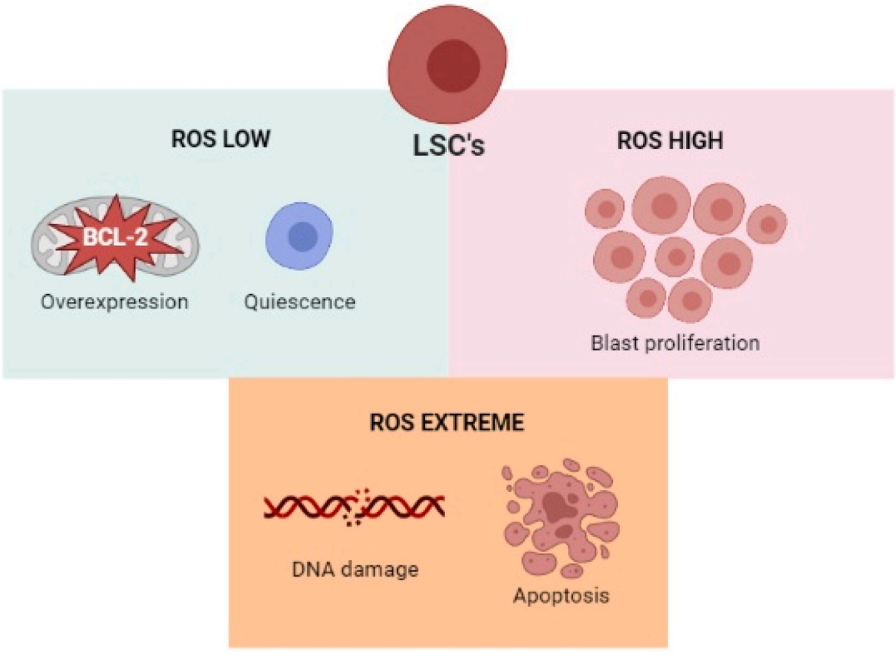

Fig. 2. The behavior of LSCs against different levels of ROS.

1.3. Emerging drugs targeting oxidative stress to eliminate AML LSCs

Some drugs have been reported as pro-oxidant agents causing selective cell death against AML LSCs and have been discussed in this section as emerging drug therapies in AML patients. Table 2 summarizes the selected drugs. Among them, venetoclax is the only one in clinical use to treat AML patients, and navitoclax, chidamide, fenretinide, hydroxychloroquine, karonudib, niclosamide and triptolide are under clinical trials (Table 3).

1.4. Synthetic small molecules

1.4.1. BCL-2 inhibitors

As mentioned above, the different ROS levels found in AML LSCs interfere with some cellular characteristics as well as drug responsiveness. $CD34^+$ AML cells exhibit low levels of ROS, showing increased expression of genes related to stress, drug resistance and poor prognosis [117]. Furthermore, $CD34^+$ AML cells with low ROS levels exhibited increased sensitivity to BCL2 inhibitors, including venetoclax (also known as ABT-199), navitoclax (also known as ABT-263) and ABT-737. These small molecules reduce OXPHOS, increase ROS and selectively eliminate AML LSCs [107,117,118].

Venetoclax is a United States Food and Drug Administration (US-FDA)-approved highly selective molecule that was designed to specifically target the BH3 domain of BCL2 [119]. Although venetoclax alone has only modest clinical efficacy in AML, it achieves high response rates when combined with azacitidine or low-dose cytarabine [120,121]. Many AML patients, on the other hand, do not respond or develop resistance to venetoclax treatment because their AML LSCs can also use fatty acid oxidation (FAO) to feed OXPHOS [122–124].

More recently, Hoang et al. [125] reported that venetoclax combined with arsenic trioxide enhanced apoptosis in AML LSCs derived from both venetoclax-sensitive and venetoclax-resistant primary AML cells. In particular, Cho et al. [126] reported that arsenic trioxide synergistically promotes venetoclax anti-AML LSC effects by downregulating Mcl-1.8-Chloro-adenosine [122,127] and CDK7 inhibitors [128] have also been reported to enhance the anti-AML LSC activity of venetoclax.

Lachowiez et al. [129] reported a clinical trial evaluating the efficacy and safety of the intensive chemotherapy and venetoclax combination regimen compared with the intensive chemotherapy alone regimen in patients with AML. After a 30-month follow-up, the venetoclax plus intensive chemotherapy cohort had an MRD-negative composite complete response rate of 64 (86%) of 74 patients, compared to 86 (61%) of 140 patients in the intensive chemotherapy cohort. Although the overall survival did not significantly differ between these two cohorts, venetoclax plus intensive chemotherapy improved event-free survival.

Table 2
Drugs that target oxidative stress to eliminate AML LSCs.

Drugs	Oxidative stress-associated mechanism	References
2-methoxyestradiol	HIF-1α inhibition	[154]
3-Deazaneplanocin A	Histone methyltransferase inhibition Thioredoxin inhibition	[134]
4-benzyl,2-methyl,1,2,4-thiadiazolidine	GSK3b inhibition PKC inhibition FLT3 inhibition	[141]
4-hydroxy-2-nonenal	NF-kB inhibition	[153]
ABT-737	BCL-2 inhibition	[107]
Avocatin B	Fatty acid β-oxidation inhibition	[150]
Celastrol	NF-kB inhibition	[153]
Chidamide	Histone deacetylase inhibition JNK inhibition NF-kB inhibition	[135]
Diosmetin	Estrogen receptor inhibition	[155]
Disulfiram/copper	JNK activation NF-kB inhibition	[131]
Fenretinide	NF-κB inhibition Wnt inhibition	[139,140]
GNPIPP12MA	FTO inhibition	[133]
Hydroxychloroquine	Autophagy inhibition	[138]
Karonudib (also known as TH1579)	MTH1 inhibition	[108]
Mefloquine	Lysosomal disruption	[142]
Micheliolide	NF-kB inhibition	[149]
Navitoclax (also known as ABT-263)	BCL-2 inhibition	[107]
Niclosamide	NF-kB inhibition	[132]
Oridonin	Thioredoxin inhibition Thioredoxin reductase inhibition	[159]
Parthenolide	NF-κB inhibition / p53 activation	[144]
Peperomin E	Thioredoxin reductase inhibition	[157]
Piplartine	Glutathione inhibition	[142]
Triptolide	HIF-1α inhibition	[152]
Venetoclax (also known as ABT-199)	BCL-2 inhibition	[117]

1.4.2. Disulfiram/copper

Disulfiram is a U.S. FDA-approved drug to treat alcoholism that acts as an aldehyde dehydrogenase inhibitor. The action of disulfiram combined with copper was studied in three AML cell lines, KG-1, NB4 and U-937. This combination caused disruption of ROS balance, cell cycle arrest and apoptosis in AML cells along with increased expression of the tumor suppressor FOXO and decreased expression of the MYC oncogene [130].

Xu et al. [131] demonstrated the antileukemic activity of disulfiram in combination with copper, where these compounds exhibited the ability to target $CD34+CD38^-$ LSC-like cells sorted from AML KG-1a and Kasumi-1 cell lines, as well as primary $CD34^+$ AML samples. Apoptotic cell death induction and suppression of colony formation were observed in disulfiram/copper-treated AML cells but not in their normal counterparts. These effects were associated with oxidative stress by activating the ROS-JNK pathway and inhibiting NF-kB signaling.

1.4.3. Niclosamide

Niclosamide is an orally bioavailable chlorinated salicylanilide approved by the US-FDA as an anthelmintic agent. In a study performed by Jin et al. [132], niclosamide was able to induce cell death in the $CD34+CD38^-$ subpopulation from AML primary cells, preserving those from normal bone marrow. Increased ROS and inhibition of NF-kB signaling were also found in niclosamide-treated AML HL-60 cells. Elimination of ROS by the glutathione precursor *N*-acetylcysteine decreased niclosamide-induced apoptosis, suggesting that niclosamide increased ROS levels to induce apoptosis in AML HL-60 cells. In *nu/nu* BALB/c mice bearing HL-60 xenografts, niclosamide (40 mg/kg) inhibited tumor growth and NF-kB signaling.

1.4.4. GNPIPP12MA

A study developed a treatment strategy against AML LSCs based on bioprinted GSH nanocomposites loaded with an N6-methyladenosine (m6A) fat mass and obesity-associated (FTO) demethylase inhibitor (GNPIPP12MA) with the aim of achieving synergistic GSH depletion of the FTO/m6A pathway and consequently targeting leukemia development. GNPIPP12MA was able to target AML Kasumi-1 and $CD34+CD38^-$ AML cells, leading to cell death by ferroptosis in a ROS-dependent mechanism with low effect in cells from normal bone morrow. It was also effective in the AML C1498 mouse model and increased the effect of the anti-PDL-1 antibody in this in vivo model [133].

1.4.5. 3-Deazaneplanocin A

3-Deazaneplanocin A is a histone methyltransferase inhibitor that induces disruption in polycomb-repressive complex 2 (PRC2), causing apoptosis in cancer cells. Zhou et al. [134] demonstrated that

Table 3
Drugs that target oxidative stress to eliminate AML LSCs and are tested in clinical trials as anti-AML therapy.

ID	Study Title	Conditions	Interventions	Phase	First Posted	Current Status
NCT05305859	Venetoclax Combining Chidamide and Azacitidine (VCA) in the Treatment of R/R AML	Leukemia, Myeloid, Acute Relapsed Adult AML Refractory Leukemia	Drug: venetoclax combining chidamide and azacitidine (VCA)	Phase 2	March 31, 2022	Recruiting
NCT05330364	Study of Chidamide Combined With Cladribine in Refractory/Relapsed Acute Myeloid Leukemia	Acute Myeloid Leukemia	Drug: Chidamide Drug: Cladribine	Phase 2	April 15, 2022	Recruiting
NCT05603884	VCA Regimen Followed by D-MAG Regimen on the Treatment of Elderly Patients With Newly Diagnosed Acute Myeloid Leukemia (AML)	Leukemia, Myeloid, Acute AML Stage, Adult	Drug: Venetoclax Combining Chidamide and Azacitidine (VCA) regimen followed by dicitabine combined with liposome mitoxantrone, cytarabine, and G-CSF (D-MAG) regimen	Phase 2	November 3, 2022	Not yet recruiting
NCT02886559	Chidamide Plus DCAG for Relapsed/ Refractory AML	AMLRelapse	Drug: Chidamide plus DCAG regimen	Phase 1 Phase 2	September 1, 2016	Unknown
NCT03031262	Efficacy and Safety of Chidamide in CBF Leukemia	AML	Drug: Cytarabine Drug: Chidamide	Phase 1 Phase 2	January 25, 2017	Unknown
NCT03985007	CDIAG Regimen in the Treatment of Relapsed or Refractory Acute Myeloid Leukemia	Acute Myeloid Leukemia, Relapsed, Adult	Drug: CDIAG regimen	Phase 2	June 13, 2019	Completed
NCT05029141	New Double Epigenetic Regimen in the Treatment of Relapsed or Refractory Acute Myeloid Leukemia	Acute Myeloid Leukemia Refractory Acute Leukemia Relapsed Adult AML	Drug: CAHAG regimen Drug: Placebo regimen	Phase 2	August 31, 2021	Active, not recruiting
NCT05659992	Clinical Study of Venetoclax Combined With CACAG Regimen in the Treatment of Newly Diagnosed Acute Myeloid Leukemia	Acute Myeloid Leukemia	Drug: azacytidine; cytarabine; aclamycin; Chidamide; venetoclax; granulocyte	Phase 1	December 21, 2022	Recruiting
NCT03453255	DCHA as Postremission Therapy for AML With t(8; 21)	Chemotherapy	Drug: Chemotherapy	Phase 1 Phase 2	March 5, 2018	Unknown
NCT05682755	Chidamide Prevents Recurrence of High-risk AML After Allo-HSCT	Leukemia, Myeloid, Acute	Drug: Chidamide	Phase 1 Phase 2	January 12, 2023	Recruiting
NCT05270200	Single Arm Study of Post-transplant Azacitidine and Chidamide for Prevention of Acute Myelogenous Leukemia Relapse	Leukemia, Myeloid, Acute	Drug: Azacitidine Drug: Chidamide	Phase 1 Phase 2	March 8, 2022	Recruiting
NCT01187810	Fenretinide in Children With Recurrent/Resistant ALL, AML, and NHL	Acute Myelogenous Leukemia Acute Lymphoblastic Leukemia Non-Hodgkin's Lymphoma	Drug: Fenretinide Drug: Cytarabine Drug: Methotrexate	Phase 1	August 24, 2010	Terminated (drug supply)
NCT00104923	Fenretinide in Treating Patients With Refractory or Relapsed Hematologic Cancer	Chronic Myeloproliferative Disorders Leukemia Lymphoma Multiple Myeloma and Plasma Cell Neoplasm	Drug: fenretinide	Phase 1	March 4, 2005	Completed
NCT02631252	Phase I Study of Mitoxantrone and Etoposide Combined With Hydroxychloroquine, for Relapsed Acute Myelogenous Leukemia	Leukemia, Acute Myelogenous	Drug: Hydroxychloroquine Drug: Mitoxantrone Drug: Etoposide	Phase 1	December 16, 2015	Terminated (Inability to accrue)
NCT04077307	A Study in Leukemia Patients With Karonudib (MAATEO)	Leukemia	Drug: Karonudib	Phase 1	September 4, 2019	Unknown
NCT05222984	Navitoclax, Venetoclax, and Decitabine for the Treatment of Relapsed or Refractory Acute Myeloid Leukemia Previously Treated With Venetoclax	Recurrent Acute Myeloid Leukemia Refractory Acute Myeloid Leukemia	Drug: Decitabine Biological: Navitoclax Drug: Venetoclax	Phase 1	February 3, 2022	Recruiting
NCT05455294	Combination Navitoclax, Venetoclax and Decitabine for Advanced Myeloid Neoplasms	Myeloid Malignancy Myelodysplastic Syndromes Myelofibrosis Acute Myeloid Leukemia Myeloproliferative Neoplasm	Drug: Navitoclax Drug: Venetoclax Drug: Decitabine	Phase 1	July 13, 2022	Recruiting
NCT05188170	Niclosamide in Pediatric Patients With Relapsed and Refractory AML	Acute Myeloid Leukemia	Drug: Niclosamide	Phase 1	January 12, 2022	Recruiting
NCT03347994	Minnelide in Adult Patients With Relapsed or Refractory Acute Myeloid Leukemia	Acute Myeloid Leukemia	Drug: Minnelide	Phase 1	November 20, 2017	Withdrawn (Discordance in contractual language and terms)

*All studies were accessed at www.clinicaltrials.gov on March 28th, 2023 by using the search term "AML" and the drugs that are presented in Table 2 (with exception of venetoclax that is already in clinical use).

3-deazaneplanocin induces apoptosis in both AML cell lines and patient-derived CD34+CD38$^-$ AML-enriched subpopulations. Inhibition of thioredoxin activity and augmentation of ROS were also found in 3-deazaneplanocin A-treated AML cells.

1.4.6. Chidamide

Chidamide, a benzamide-type selective histone deacetylase (HDAC) inhibitor developed in China, induces cell cycle arrest and apoptosis in cancer cells. It induced apoptosis in AML cell lines and primary AML CD34$^+$ cells. Chidamide caused ROS-mediated apoptotic cell death by modulation of antiapoptotic and proapoptotic proteins in the BCL2 family, activation of caspase-3 and cleavage of PARP, along with downregulation of the JNK and NF-κB pathways through activation of CD40 [135].

1.4.7. Hydroxychloroquine

Hydroxychloroquine is a U.S. FDA-approved drug to treat malaria and acute and chronic inflammatory diseases, such as rheumatoid arthritis and systemic lupus erythematosus. It is also an autophagy inhibitor with the ability to induce ROS-mediated apoptosis in cancer cells [136,137]. In a study with AML LSCs performed by Folkerts et al. [138], MOLM13 and NB4 AML cell lines and primary AML CD34$^+$ cells were more sensitive to hydroxychloroquine than normal bone marrow CD34$^+$ cells. Next, primary AML CD34$^+$ cells were separated into low ROS and high ROS subtractions. Primary AML CD34$^+$ cells with low ROS levels showed higher basal autophagy and were more sensitive to hydroxychloroquine than AML CD34$^+$ cells with high ROS levels.

1.4.8. Karonudib

Karonudib (also known as TH1579) is an oral inhibitor of MTH1, an enzyme preventing oxidized dNTP incorporation in DNA. It was able to eliminate both primary blast AML and primary CD34+CD38$^-$ AML cells while sparing normal cells. Karonudib caused mitotic arrest, increased ROS levels and improved oxidative DNA damage in AML HL-60 cells. Karonudib (45 and 90 mg/kg twice daily, three times a week) inhibited AML development and enhanced survival in NSG mice transplanted intravenously with AML HL60Adp luciferase-expressing cells [108].

1.4.9. Fenretinide

Fenretinide is a synthetic retinoid derivative with action in cancer cells. It was able to induce cell death and inhibit the formation of colonies in primary AML CD34$^+$ cells without affecting their normal counterparts. Fenretinide also caused the generation of ROS, increased stress responses and apoptosis-related gene transcripts and reduced NF-κB and Wnt signaling. It also inhibited the in vivo engraftment of AML LSCs but not HSCs [139].

Zhao et al. [140] demonstrated that it induces ROS production and NF-κB inhibition in AML MV4-11 cells. In addition, primary AML CD34$^+$ cells with FMS-like tyrosine kinase 3 (FLT3)-internal tandem duplication (ITD) mutations were more sensitive to fenretinide than those without FLT3-ITD mutations.

1.4.10. 4-Benzyl,2-methyl,1,2,4-thiadiazolidine

4-Benzyl,2-methyl,1,2,4-thiadiazolidine, a member of the thiadiazolidine class, is a non-ATP competitive inhibitor of glycogen synthase kinase 3β (GSK3b). It caused cell death in different subtypes of leukemia, including primary CD34+CD38$^-$ AML cells, without affecting HSCs. Induction of oxidative stress and inhibition of the PKC and FLT3 signaling pathways were also found in 4-benzyl,2-methyl,1,2,4-thiadiazolidine-treated primary AML cells [141].

1.4.11. Mefloquine

Mefloquine is a U.S. FDA-approved antimalarial agent. Similar to chloroquine and hydroxychloroquine, it is an autophagy inhibitor. Mefloquine induced cell death in AML cell lines, primary bulk AML cells and primary AML progenitor cells more effectively than in normal hematopoietic progenitor cells. Induction of oxidative stress and lysosomal disruption were found in mefloquine-treated TEX and OCI-AML2 cells. Mefloquine also showed antileukemic activity on mouse leukemic MDAY-D2 cells and human leukemic OCI-AML2 or K562 cells (50 mg/kg daily by oral gavage), as well as on primary human AML cells (100 mg/kg daily by oral gavage) growing in xenografted mice [142].

1.5. Natural product compounds

1.5.1. Parthenolide and analogs

Parthenolide, a natural component extracted from the species *Tanacetum parthenium*, has been identified to inhibit the ability of LSCs to respond to oxidative stress by making LSCs sensitive to cell death [143]. It induced robust apoptosis in primary human AML cells and blast crisis CML cells while sparing HSCs. When compared to cytarabine chemotherapy, parthenolide is much more specific for leukemia cells. It also induced NF-κB inhibition, proapoptotic activation of the tumor suppressor p53 and increased production of ROS, suggesting that this molecule activity triggers LSC-specific apoptosis [144]. Furthermore, Kim et al. [145] demonstrated that parthenolide activity is greater in cell lines with high myeloperoxidase leukemia than in cell lines with low myeloperoxidase leukemia.

In contrast, parthenolide has poor pharmacological properties, limiting its potential clinical use. Therefore, many parthenolide analogs have been synthesized and evaluated against leukemia cells. Dimethylamino-parthenolide, an orally bioavailable parthenolide analog, caused cell death in human primary LSCs from both myeloid and lymphoid leukemias and was cytotoxic to bulk leukemic cells. It also induces oxidative stress, inhibits NF-kB signaling and activates the p53 pathway [146]. A C1–C10-modified parthenolide analog was also found to inhibit AML LSCs along with improved ROS induction and less toxicity to healthy bone marrow cells [147]. Darwish et al. [148] developed PLGA-antiCD44-parthenolide nanoparticles with enhanced bioavailability and selectivity to target AML cells.

1.5.2. Micheliolide

Micheliolide is a guaianolide sesquiterpene lactone isolated from *Michelia compressa* and *Michelia champaca* that is structurally related to parthenolide. It caused apoptosis in AML KG-1a cells, primary bulk AML cells and primary CD34+CD38$^-$ AML cells but not in HSCs. These effects were associated with inhibition of NF-κB signaling and generation of intracellular ROS. Micheliolide derivative DMAMCL administered orally at doses of 25, 50 and 100 mg/kg for seven treatments every other day increased survival in mice xenotransplanted with primary human AML cells [149].

1.5.3. Avocatin B

Avocatin B is an avocado-derived lipid mixture containing avocadene and avocadyne (two 17-carbon polyhydroxylated fatty alcohols). It is a fatty acid β-oxidation inhibitor that induces cell death in AML cell lines, primary bulk AML and progenitor AML cells without affecting HSCs. Avocatin B inhibited fatty acid oxidation and decreased NADPH levels in AML TEX cells, resulting in ROS-dependent apoptotic cell death. These effects were related to the CPT1 enzyme, which facilitates the lipid transport of mitochondria [150].

1.5.4. Triptolide

Triptolide, a diterpenoid triepoxide from the medicinal plant *Tripterygium wilfordii* Hook F, has attracted extensive exploration due to its multiple biological activities [151]. Triptolide demonstrated the ability

to induce apoptosis in CD34+CD38$^-$ LSC-like cells sorted from AML KG-1a cells. Moreover, triptolide enhanced the proapoptotic effect of idarubicin, increased the levels of ROS and decreased the colony-forming ability of CD34+CD38$^-$ LSC-like cells from AML KG-1a cells. A reduction in the expression of Nrf2 and HIF-1α was also observed in cells treated with the combination of triptolide and idarubicin [152].

1.5.5. Celastrol

Celastrol (also known as tripterine) is a pentacyclic nortriterpene quinone isolated from the root of *Tripterygium wilfordii* and *Tripterygium regelii*. Celastrol was selected by in silico study due its similar properties to parthenolide. It was able to eliminate bulk primary AML as well primary CD34+CD38$^-$ AML cells with less effect on HSCs. Celastrol also impaired engraftment of primary AML cells in immunocompromised mice. Induction of apoptosis associated with oxidative stress, Nrf2 activation and NF-kB signaling inhibition were also observed in celastrol-treated AML cells [153].

1.5.6. 4-hydroxy-2-nonenal

4-Hydroxy-2-nonenal is an α,β-unsaturated hydroxyalkenal produced in cells during oxidative stress by lipid peroxidation. Similar to celastrol, 4-hydroxy-2-nonenal was selected as an anti-AML compound for the in silico study. It also exhibited toxicity to primary AML CD34+CD38$^-$cells and impaired engraftment of primary AML cells in immunocompromised mice. 4-Hydroxy-2-nonenal also caused oxidative stress-mediated apoptosis, Nrf2 activation and inhibition of NF-kB signaling in primary AML cells [153].

1.5.7. 2-methoxyestradiol

2-Methoxyestradiol is a 17-estradiol endogenous metabolite that interacts with estrogen receptors and microtubules. Zhe et al. [154] reported that 2-methoxyestradiol is able to induce apoptosis in HL-60 and Kasumi-1 AML cell lines along with inhibition of HIF-1α and its target genes VEGF, GLUT1 and HO-1. It also reduced the CD34$^+$ cell subpopulation of bone marrow from AML patients, with a lower effect on CD34$^+$ cells from normal bone marrow, in a superior manner to cytarabine. This molecule also increased intracellular ROS, and its effect was prevented using the antioxidant N-acetylcysteine.

1.5.8. Diosmetin

Diosmetin is a flavonoid molecule from citrus fruits that has a variety of pharmacological properties. Diosmetin presented in vitro anti-AML activity against a panel of AML cell lines (KG-1a, U937, OCI-AML2 and TEX) and impaired engraftment of TEX cells in immunocompromised mice. Mechanistically, diosmetin is an estrogen receptor β (ERβ) agonist. In particular, primary AML cells with high levels of ERβ were more sensitive than primary AML cells with low ERβ. Interestingly, knockdown of ERβ induced resistance to diosmetin cytotoxicity, while ERβ overexpression improved sensitivity to diosmetin. This effect was associated with the activation of ROS signaling. Moreover, diosmetin (50 mg/kg every other day) administered for 6 weeks reduced engraftment of primary AML cells but not HSCs in immunocompromised mice [155].

1.5.9. Peperomin E

Peperomin E, a secolignan isolated from the Chinese medicinal plant *Peperomia dindygulensis* (Piperaceae), has been reported to selectively and effectively target and initiate oxidative stress-induced apoptosis in KG-1a CD34+CD38$^-$ cells [156].

Peperomin E and its orally bioavailable analog 6-methyl(hydroxyethyl)amino-2,6-dihydropeperomin E also eliminate KG-1a CD34$^+$ cells and primary CD34$^+$ AML cells. 6-Methyl(hydroxyethyl)amino-2,6-dihydropeperomin E (25 and 50 mg/kg/day for 5 weeks) reduced the growth of KG-1a CD34$^+$ cells in immunocompromised mice. It also induced oxidative stress-mediated apoptosis in KG-1a CD34$^+$ cells through inhibition of thioredoxin reductase [157].

1.5.10. Oridonin

Oridonin, a diterpene extracted from the species *Rabdosia rubescens*, caused apoptotic cell death in t(8; 21) leukemia cells, induced cleavage of the AML1-ETO oncoprotein resulting from t(8; 21) and reduced tumor growth in immunocompromised mice inoculated with t(8; 21)-harboring Kasumi-1 cells [158]. Oridonin also selectively induced ROS-mediated apoptosis by directly binding to glutathione and inhibiting thioredoxin/thioredoxin reductase in t(8; 21) AML cells. Inhibition of c-Kit + AML LSCs in bone marrow from AML1-ETO9a leukemia mice was also observed after treatment with oridonin in vitro and in vivo [159].

1.5.11. Piplartine

Piplartine, also known as piperlongumine, is a natural molecule from the genus *Piper* with multiple activities [160–166]. Investigating a targeted therapy based on the eradication of CD34$^+$ AML cells that have acquired aberrant glutathione metabolism, Pei et al. [143] used agents known to act directly on the aberrant glutathione pathway, such as piplartine and/or piplartine, in combination with cytarabine and idarubicin in AML cells. Their work demonstrated that these compounds were able to induce glutathione depletion and lead to a reduction in the primary AML CD34+CD38$^-$subpopulation.

2. Conclusion

As we discuss in this review, oxidative stress has both tumor-promoting and tumor-suppressing functions. Under low conditions, ROS participate in the self-renewal of HSCs, while an increase in the level of ROS is necessary for the proliferation and differentiation of HSCs, but excessive levels of ROS induce oxidative damage to cellular DNA and proteins, resulting in cell death or favoring the development of AML. In AML, a low level of ROS is related to the quiescence of LSCs, while a high level of ROS is found in AML blasts and participates in cell proliferation. In both cases, the increase in ROS in AML bulk and/or AML LSCs can induce apoptotic death and suppress AML cell proliferation. Currently, there are some potential drugs able to eliminate AML LSCs via ROS increase and, consequently, reduce the probability of disease recurrence. Among them, navitoclax, chidamide, fenretinide, hydroxychloroquine, karonudib, niclosamide, and triptolide are under clinical trials, and venetoclax is a drug approved by the US-FDA to treat patients with AML. Future research targeting oxidative stress as an efficient approach to eradicate AML LSCs should be undertaken.

Authors' contributions

RGAC, SLRS and IRSBD drafted the content of the cellular redox homeostasis subtopic. RGAC, SLRS, IRSBD and ACBCR drafted the content of the pleiotropic effect of oxidative stress in the AML subtopic. RGAC, SLRS and MSO drafted the content of emerging drugs targeting oxidative stress to eliminate AML LSCs subtopic. RBD and DPB planned this review and reviewed the whole text. All authors read and approved the final manuscript.

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.

Data availability

No data was used for the research described in the article.

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Abbreviations:

AML	acute myeloid leukemia
CAT	catalase
CDKs	cyclin-dependent kinases
ERβ	estrogen receptor β
ETC	electron transport chain
FAB	French-American-British
FAO	fatty acid oxidation
FLT3	FMS-like tyrosine kinase 3
FTO	fat mass and obesity associated
GPx	glutathione peroxidase
GRx	glutathione reductase
GSH	reduced glutathione
GSK3b	glycogen synthase kinase 3β
GSSG	oxidized glutathione
GST	glutathione-S-transferase
HDAC	histone deacetylase
HSCs	hematopoietic stem cells
ITD	internal tandem duplication
LSCs	leukemia stem cells
m6A	N6-methyladenosine
MRD	minimal residual disease
NADPH	nicotinamide adenine dinucleotide phosphate
NOX2	NADPH oxidase 2
OXPHOS	oxidative phosphorylation system
PRC2	polycomb-repressive complex 2
PRXs	peroxiredoxins
RNS	reactive nitrogen species
ROS	reactive oxygen species
RSS	reactive sulfur species
SODs	superoxide dismutases
SORs	superoxide reductases
TrxR	thioredoxin reductase
TXNIP	thioredoxin-interacting protein
US-FDA	United States Food and Drug Administration
WHO	World Health Organization

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