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REVIEW ARTICLE

Effects of Berberine on Leukemia with a Focus on Its Molecular Targets

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Abstract: Leukemia is common among both women and men worldwide. Besides the fact that finding new treatment methods may enhance the life quality of patients, there are several problems that we face today in treating leukemia patients, such as drugs' side effects and acquired resistance to chemotherapeutic drugs. Berberine is a bioactive alkaloid found in herbal plants (*e.g.*, Rhizoma coptidis and Cortex phellodendri) and exerts several beneficial functions, including anti-tumor activities. Furthermore, berberine exerts antiproliferative and anti-inflammatory effects. Up to now, some studies have investigated the roles of berberine in different types of leukemia, including acute myeloid leukemia and chronic lymphocytic leukemia. In this review, a detailed description of the roles of berberine in leukemia is provided. We discuss how berberine involves different molecular targets (*e.g.*, interleukins and cyclins) and signaling pathways (*e.g.*, mTOR and PI3K) to exert its anti-tumor functions and how berberine is effective in leukemia treatment when combined with other therapeutic drugs.

Keywords: Berberine, leukemia, apoptosis, proliferation, autophagy, inflammation.

1. INTRODUCTION

Based on the American Cancer Society statistics, the estimated new cases of leukemia and its estimated deaths in 2021 are reported to be 61,090 and 23,660 respectively [1]. There are different types of leukemia, but four of them are more common, including myelodysplastic syndrome, myeloproliferative neoplasm, chronic myeloid leukemia (CML), and acute myeloid leukemia (AML) [2, 3]. CML, a malignant clonal hematological disease, is defined by the myeloid neoplastic cells spread into the blood circulation and bone marrow [4]. Another common type of leukemia is chronic lymphocytic leukemia (CLL), which is the disease of the elderly with a median age of 72 years [5]. Leukemia risk factors are classified into four categories: familial, genetic, environmental, and lifestyle risk factors. Benzene, formaldehyde, 1,3 butadiene, high dose ionizing radiation, chemotherapeutic drugs, and electromagnetic fields are some of the environmental risk factors. Smoking, obesity, and dietary intake are some of the lifestyle risk factors [6, 7]. 5-year relative survival of patients varies from type to type. While 5-year survival is 27.4% in AML patients, this number rises to 84.2% for CLL patients [8]. Besides, more than half of patients surviving the disease relapse after treatment [9]. Therefore, new treatment modalities are essential for patients with leukemia.

Berberine, a phytochemical compound, is mostly extracted from roots, rhizome, and stem bark of barberry [10]. In recent years, berberine has been discovered to have a variety of pharmacological and biological activities such as antimicrobial, anti-helminthic, anti-inflammatory, and anti-oxidative effects [11]. Furthermore, several studies have investigated the anti-cancer activities of berberine [11]. In this review, a detailed description of berberine roles in leukemia is provided. We discuss how berberine involves different molecular targets and signaling pathways to exert its anti-tumor functions.

2. PATHOGENESIS OF LEUKEMIA

In acute leukemia, the abnormal blood cells are usually blasts that remain immature. Consequently, fail to perform their expected functions. Acute leukemia exhibits fast development and requires immediate attention. In chronic leukemia, there are also some blast cells. However, these blast cells are different from cells presented in acute leukemia. Indeed, they are more mature and may still have their normal functions [12]. The progression of chronic leukemia is usually much slower than acute leukemia and may not need immediate treatment. Based on another type of classification, leukemia can be divided into two types according to the affected cells, lymphoblastic leukemia and myeloid leukemia. In lymphoblastic leukemia, the malignant changes involve a type of bone marrow cells that eventually become lymphocytes. In myeloid leukemia, the malignant changes involve the type of bone marrow cells that eventually become red blood cells, some other types of white cells, and platelets [12]. These two types of divisions lead to four major subtypes in total, including ALL, CLL, AML, and CML. CML is a stem cell disorder characterized by the proliferation of hematopoietic stem cells due to the BCR-ABL fusion oncogene, resulting in reciprocal translocation t(9;22) (q34;q11). It is known that imatinib, a tyrosine kinase inhibitor that blocks the breakpoint cluster region protein/ Abelson murine leukemia viral oncogene homolog (BCR-ABL1) leads to the suppression of PI3K/AKT, JAK/STAT, and RAS/RAF/MEK/ERK pathways [3]. CLL is an incurable neoplastic disorder that is the most common form of leukemia. It is character-

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ized by a gradual accumulation of small and mature B cells with typical B-cell markers, including CD5, CD19, CD23, and CD20 [13]. ALL is caused by the accumulation and proliferation of lymphoid progenitor cells in different tissues, including bone marrow [14]. In AML, myeloid stem cells are abnormally proliferated and differentiated. What changes the normal maturation of myeloid precursors can be some translocations in the chromosome, including t(8:21) in core-binding factor AML [15]. Treatment for AML is chemotherapy with cytarabine and anthracycline or hypomethylating 0.agents and allogeneic hematopoietic stem cell transplant [16, 17].

3. OXIDATIVE STRESS IN LEUKEMIA

Oxidative stress results from a biochemical imbalance consisting of excessive production of reactive oxygen species (ROS) and nitrogen species, leading to oxidative damage to biomolecules and cannot be defused by anti-oxidative systems [18]. ROS are a group of heterogeneous molecules that are generated by mature myeloid cells throughout innate immune responses. The imbalance in production and degradation of ROS is the definition of oxidative stress which has been observed in some malignancies such as leukemia [19, 20]. The activity of ROS is a major part of cell function. While irregularities in ROS levels result in DNA impairment. Moreover, higher levels of ROS cause changes in the metabolic state of cells [21]. ROS role in oxidative stress is through influencing intracellular cascades such as mitogen-activated protein kinases (MAPKs), phosphatidyl inositol-3-kinase (PI3K/Akt), phospholipase C-g1, protein kinase C, nuclear factor-jB (NF-jB), and Janus kinase/signal transducer and activator of transcription (JAK/STAT). ROS prompts the expression of heat shock proteins (Hsp27), immediate early genes (c-jun and c-fos), and hypoxia-inducible factors. Also, ROS affects antioxidant enzymes, which are involved in redox homeostasis, transforming oncoproteins, and growth factors [22].

4. INFLAMMATION AND LEUKEMIA

Inflammation and inflammatory cytokines have always been a major reason for the onset and progression of leukemia [23]. Pro-Inflammatory agents like IL-1, IL-6, IL-15, IL-17, IL-23, and TNFα have a role in leukemia severity. On the other hand, anti-inflammatory mediators like IL-4, IL-10, IL-13, transforming growth factor (TGFβ), and interferon α (IFNα) seem to inhibit the progression of leukemia. These complex interactions among pro- and anti-inflammatory cytokines make a carcinogenetic microenvironment that influences cell proliferation and survival in leukemia [13, 24]. The major function of TNFα is to activate NF-κB. Meanwhile, IL-10 deactivates NF-κB, which promotes pro-inflammatory cytokine TNFα, IL-6, and IL-12 [13]. IL-6 can trigger the expression of miR-21, which is an inflammatory stimulus. TNFα and IFN-β stimulate the expression of miR-155 and its increased levels are found in the bone marrow of leukemia patients and cause hyperproliferation of B-cells [13].

5. BERBERINE

Berberine (chemical formula: $C_{20}H_{18}NO_4$) is a bioactive isoquinoline alkaloid that exists in herb plants, such as Cortex phellodendri and Rhizoma coptidis [25, 26]. Rutaceae, Berberidaceae, and Papaveraceae are other sources of berberine. Berberine was at first used as a broad-spectrum antibacterial drug. Pharmacological uses such as antibacterial, anti-inflammatory, antihypertensive, hypolipidemic, and antidiarrheal effects were the main applications of berberine in the past [27]. Berberine is also an antioxidant and anti-inflammatory agent. By exerting anti-oxidative and anti-inflammatory functions, berberine could be effective in type 2 diabetes and cardiovascular diseases' management (Fig. **1**) [28]. Berberine affects the development of tumor cells by inhibiting the growth of tumor cells as well as stimulating apoptosis and cell cycle arrest [29-33]. Berberine lowers plasma LDL by increasing LDLR mRNA expression at a post-transcriptional level [34]. The main organ for berberine metabolism is the liver. The major cytochrome P450 (CYPs) for producing berberine metabolites is CYP2D6. CYP1A2, 3A4, 2E1, and CYP2C19 are enzymes that are also involved in berberine metabolism [35, 36]. It has been discovered that berberine could increase the activity of AMP-activated protein kinase, which leads to phosphorylation of the tumor suppressor gene p53 in vascular smooth muscle cells as well as growth inhibition and apoptosis in non-small cell human lung cancer cells [11]. Besides the advantages of berberine, there are some limitations, such as poor aqueous solubility, slight absorption, and low bioavailability. To overcome these limitations, the utilization of nanotechnology-based platforms (such as nanoparticles, hydrogels, and micelles) and various analogs are suggested (Fig. **1**) [32].

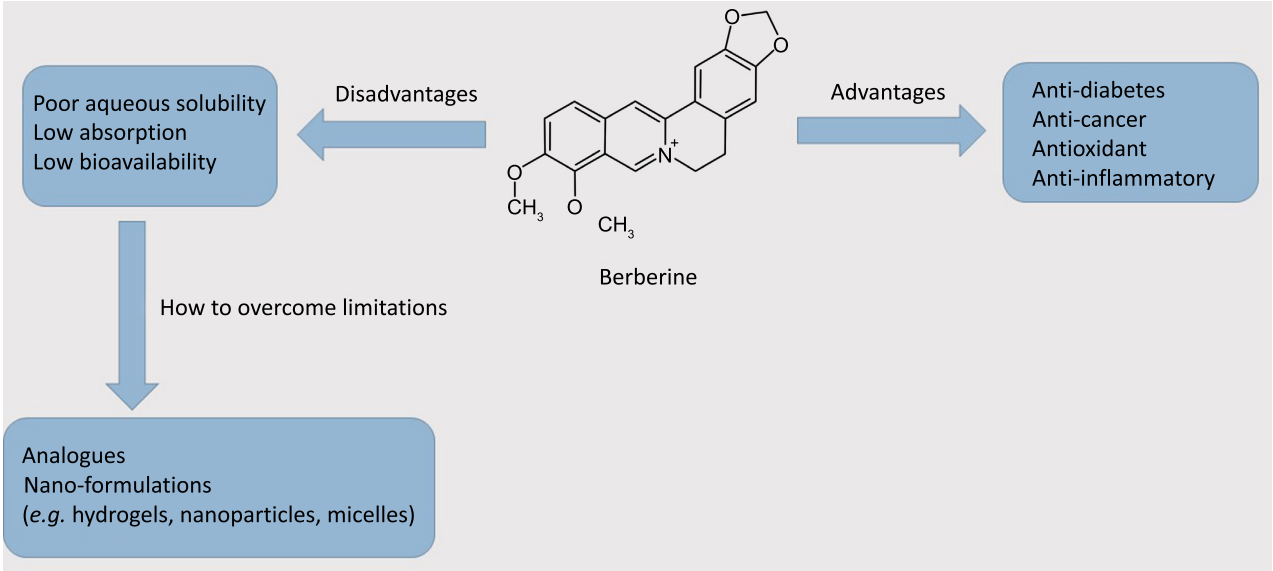

Fig. (1). Different advantages and disadvantages of berberine. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

6. ANTI-INFLAMMATORY AND ANTIOXIDANT EFFECTS OF BERBERINE

Several studies have investigated the anti-inflammatory role of berberine in various diseases. Berberine is reported to reduce the expression levels of various pro-inflammatory cytokines, including IL-6, IL-8, IL-13, IFN-γ, and TNF-α [37]. Berberine can also modulate the tight junction damage of intestinal epithelium, which is induced by pro-inflammatory cytokines [38, 39]. In chronic respiratory diseases, berberine exerts anti-inflammatory effects *via* different signaling pathways, including p38 MAPK, NF-κB, and ERK1/2 [40]. Moreover, in non-alcoholic fatty liver disease of rats, berberine is reported to suppress the inflammatory response by regulating the Angptl2 pathway [41]. Therefore, berberine attenuates inflammatory processes through various mechanisms.

Berberine is shown to increase the hepatic antioxidant enzymes in thioacetamide-induced liver fibrosis, leading to the suppression of hepatic fibrosis [42]. Another study has reported that berberine exerts protective effects on PC-12 cells against oxidative damage by suppressing ROS through PI3K/AKT/mTOR pathway [43]. Berberine is capable of enhancing the activities of glutathione peroxidase and catalase enzymes in mice intestinal tissue, resulting in reduced oxidant status [44]. Moreover, berberine modulates the formation of ROS in spiral ganglion cells [45]. Altogether, these pieces of information indicate that berberine is a potential antioxidant agent which enhances antioxidant status by different mechanisms [46].

7. BERBERINE AND LEUKEMIA

Findings have shown that berberine exerts multiple functions in leukemia; thus, it can be used as an antitumor agent for treating this cancer. However, the exact underlying mechanisms of berberine's function in leukemia are to be elucidated. Herein, we take a look at the details provided by research until now, aiming to provide an insight into which areas are not paid attention to enough and which areas are well-understood.

Development and progression of tumors as well as their malignant features, such as changes in differentiation of cells, instabilities in the genome, and increased metastatic abilities, have been related to P53 dysfunction [47, 48]. Mutation of TP53 happens in approximately 8% of de novo AML cases. Besides, Li-Fraumeni syndrome-related AML is also rare. Thus, other p53 abnormalities that are non-mutational may be involved in AML and other types of leukemia. In fact, evidence has shown that non-mutational dysfunction of wtp53 may happen in almost all subsets of AML [49]. Mouse double minute-2 (MDM2) is a regulator of P53, which provides stability and cellular localization of P53. The interaction between P53 and MDM2 induces proteasomal degradation of P53, leading to an inhibition of its transcriptional activity [50, 51]. Some studies indicate that MDM2 can be a potential target for treating ALL [52]. In a study on P53-null leukemic cells, berberine has been shown to reduce the mRNA level of MDM2 as well as increasing self-ubiquitination of MDM2 [53]. While 100 μM of berberine induces autophagy and apoptosis in leukemic cells, 3-methyladenine, which is an inhibitor of autophagy, reverses the berberine effect on autophagy [53]. Besides, forcing cells to overexpress MDM2 has an unfavorable impact on berberine-induced effects, such as autophagy, apoptosis, and doxorubicin-related effects [53]. Noteworthy, it is suggested that MDM2 reverse effects on berberine are not dependent on P53 [53]. Suppression of XIAP by berberine in p53-null leukemia cells leads to downregulation of XIAP protein and inhibition of MDM2 expression [54]. Moreover, western blot analysis showed that XIAP suppression by berberine enhances doxorubicin-induced apoptosis [54]. On the other hand, another study has shown that berberine apoptotic effects are related to MDM2 and P53 [55]. Contrary to doxorubicin, which results in the activation of P53 and MDM2 upregulation, berberine downregulates MDM2 besides the activation of P53 [55]. Moreover, berberine-induced downregulation of MDM2 has been linked to the death domain associated protein (DAXX) [55]. It is also suggested that berberine can be beneficial in the chemo-resistant form of leukemia since these cells overexpress MDM2 [55].

Proviral integration of Moloney virus-2 (PIM-2) is an anti-apoptotic factor and a member of the serine/threonine kinase family [56]. Cytokines, which are involved in hematopoietic cells maturation, are responsible for the regulation of PIM-2 expression [57]. Evidence reveals that PIM-2 is overexpressed in AML and ALL [56]. Overexpression of PIM-2 has been associated with overall survival in patients with AML [56]. Furthermore, PIM-2 downregulation inhibits the proliferation of leukemia cells [58]. PIM-2 is also a direct target of miR-24-3p [59]. In a recent study, Wang *et al*. [59] reported that treating cells with 50 μM of berberine for 24 hours can affect PIM-2 by increasing miR-24-3p. It is indicated that berberine plays anti-tumor roles by inducing apoptosis and reducing the viability of ALL cells through downregulating XIAP in P53-null and P53-mutant cells, as shown by qRT-PCR. Besides, berberine effects on apoptosis are reversed by blocking miR-24-3p or PIM-2 [59].

As we mentioned earlier, imatinib is a tyrosine kinase inhibitor that is used for the treatment of CML by reducing BCR-ABL transcripts [60]. However, it is observed that patients may develop resistance to imatinib during their treatment course due to the subclones which bear BCR-ABL mutations [61]. Berberine is shown to bind to a domain of BCR-ABL, which is called protein tyrosine kinase (PTK) [62]. Consequently, both normal BCR-ABL transcripts and BCR-ABL transcripts with the mutation in T315I are degraded through the autophagic lysosome pathway [62]. Additionally, LRSAM1, an E3 ubiquitin-protein ligase, is involved in the mentioned process [62]. Therefore, berberine could be an effective antitumor agent in CML patients who are sensitive or resistant to imatinib. Studies implied that targeting Aryl Hydrocarbon Receptor (AHR) signaling can be useful in treating AML since this pathway is suppressed in leukemic stem cells [63]. AHR, a ubiquitous helix-loop-helix transcription factor, plays various roles in biological processes such as inflammation and cell division [64]. Furthermore, it is associated with the proliferation of normal hematopoietic progenitors. UT-7 cells that express BCR-ABL have been shown to express lower levels of AHR [64]. Berberine which is considered an AhR ligand, results in the overexpression of AHR target genes (CYP1A1 and IL1β), as evidenced by RT-PCR. Consequently, this leads to inhibition of monocytes proliferation [65]. Berberine also increases IL-10, downregulates Cdk2, and upregulates p21, p27, and p53 genes in the AML cell line [65].

Knockdown of nucleophosmin/B23 is shown to downregulate Akt/mTOR signaling pathway, leading to modulation of drug resistance [66]. This ubiquitous nuclear phosphoprotein plays various roles in cells, such as progression of the cell cycle, ribosome biogenesis, duplication of the centrosome, and cell growth [67]. Overexpression of nucleophosmin/B23 leads to the proliferation of tumor cells, differentiation blockade, and resistance to apoptosis [67]. It is suggested that nucleophosmin/B23 may have a role in controlling the cellular response to apoptosis induction in human leukemia HL-60 cells [68]. Berberine can induce apoptosis by downregulating the nucleophosmin/B23 and telomerase activity [68]. Studies conducted on rats report that berberine inhibits the release of β-hexosaminidase, histamine, IL-4, and TNF-α in basophilic leukemia cells (RBL-2H3 cells) [69]. Berberine induces arrest of the cell cycle at the G1 phase and G2/M phase in leukemia, like in other cancers [25, 26, 70]. The cell cycle arrest at the G2/M phase is sim-

ultaneous with increased levels of Wee1 and 14-3-3Û and also decreased levels of Cdc25c, CDK1, and cyclin B1 [70]. Berberine has anti-proliferative actions in leukemia cells that are implemented by inducing chromatin condensation, DNA fragmentation and triggering the activation of PARP, caspase-3, and caspase-8 without activating caspase-9 [71-73]. Berberine also inhibits the proliferation of Jurkat cells. It causes cell cycle arrest at the G1 phase *via* downregulation of cyclin D1, cyclin E, and CDC2. Berberine induces apoptosis by regulating the ephrin-B2 and VEGFR2 signaling, along with modulating the MEK/ERK and PTEN/PI3K/AKT/mTOR signaling simultaneously [65]. Berberine's anti-inflammatory effects are through MAPK and COX-2 signaling pathways, where it reduces the expression of COX-2, which leads to apoptosis in T-cell ALL. Berberine suppresses IL-2 mRNA expression and protein secretion [25, 72]. By using transwell migration chambers, it is shown that berberine has a prohibitory role in tumor cell migration in a dose-dependent manner. SDF-1, a homeostatic chemokine that signals through CXCR4, is expressed by hematopoietic tumor cells. Berberine partly inhibits AML cells migration by reducing SDF-1 protein [74]. The apoptotic effects of berberine can be done by increasing ROS and Ca^{+2} production. Furthermore, berberine decreases mitochondrial membrane potential, which leads to the release of cytochrome c and the cleavage of procaspase-3 [75]. Studies conducted *in vitro* and *in vivo* revealed that berberine inhibits the expression of NAT1 protein by affecting the mRNA in HL-60 cells [76-78].

8. STRUCTURE-RELATED ANTITUMOR ACTIVITIES OF BERBERINE

Despite berberine's various beneficial activities, there are some obstacles to applying it as an antitumor agent, such as its difficulty in penetrating cytomembrane and low lipid solubility [79-83]. Poor bioavailability is another drawback in berberine application [82]. Thus, some changes have been made to berberine in investigations for modifying and transforming its chemical structure. C-9 and C-13 are the main locations where structural changes are made to enhance the anti-cancer effects of berberine [84-91]. Accordingly, several studies have been conducted on berberine derivatives to assess the associations between structural modifications and anti-tumor functions [46].

Regarding leukemia, Okubo *et al*. [73] showed that a methylenedioxyl group on ring A is essential for better anti-cancer activities of berberine compounds since the compounds lacking this group were weaker in inhibitory activities. Furthermore, the alkylation of the hydroxyl group at C-9 position makes berberine compounds more effective.

CONCLUSION

Leukemia is a common type of cancer worldwide. Besides the fact that finding new treatment methods may enhance the life quality of patients, there are several problems that we face today in treating leukemia patients, such as drugs' side effects and acquired resistance to chemotherapy drugs. Evidence shows that berberine can be used to treat different diseases, including cancer, due to its ability to involve different signaling pathways. It is demonstrated that berberine has anti-tumor effects on various cell lines, such as induction of apoptosis, inhibiting proliferation, suppressing metastasis, anti-inflammatory activities, and induction of autophagy.

Studies suggest that berberine is a potentially effective agent for inhibiting the development and progression of leukemia (Table **1** and Fig. **2**). Berberine exerts this inhibitory role by involving several molecules and signaling pathways. Induction of apoptosis and autophagy, as well as inhibiting proliferation, are the main mechanisms by which berberine is considered a beneficial target for managing leukemia. Noteworthy, studies have shown that treating cells with berberine is not limited to one type of leukemia and it affects different leukemia cell lines, including Jurkat cells, EU-4, and HL-60. These functions of berberine on leukemia cell lines seem to involve several mechanisms that require further exploration. Studies concerning the berberine anti-tumor effects have some limitations. First of all, the underlying anticancer roles are not fully understood. Secondly, most of the studies are *in vitro*; thus, *in vivo*

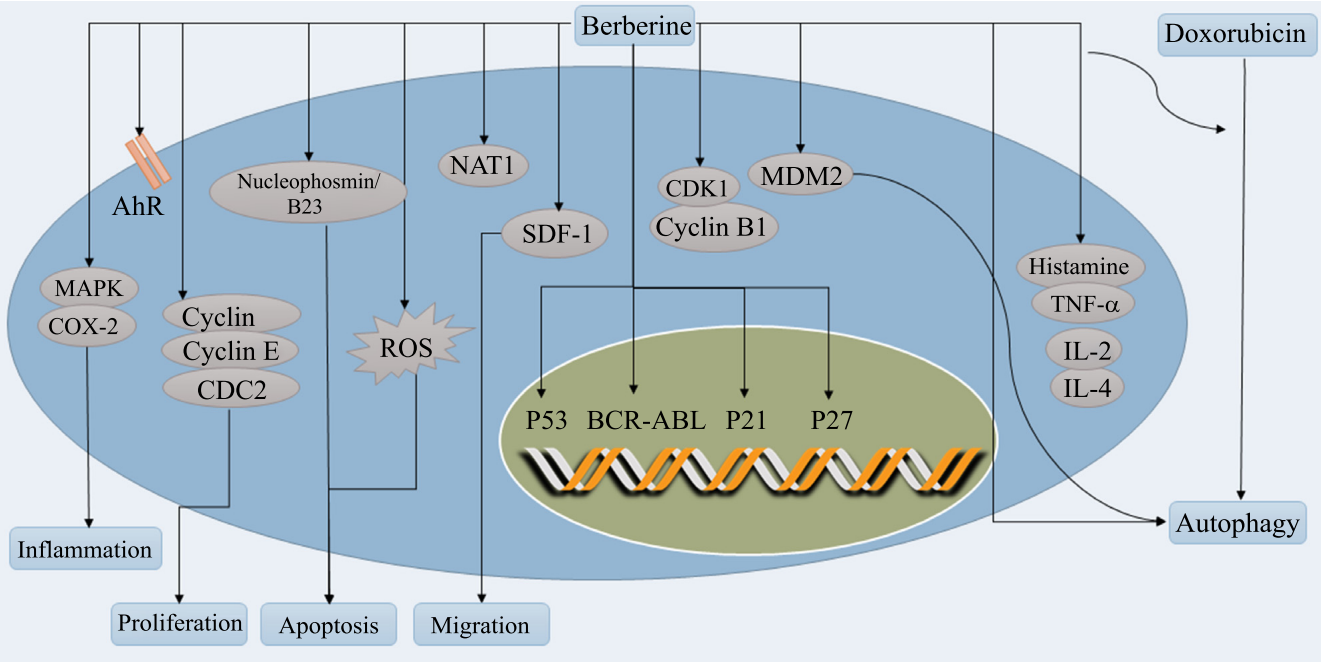

Fig. (2). Schematic representation of how berberine exerts its functions in leukemic cells. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Table 1. Studies investigated the roles of berberine in different types of leukemia.

In vivo/ *In vitro*	Dosage	Cell Line(s)	Findings	Refs.
In vitro	20 µg/ml	Jurkat	Berberine played its anti-inflammatory role possibly due to suppressing p38 MAPK expression	[25]
In vitro	6-100 µM	HL-60	Berberine iodide and acetoneberberine presented apoptosis-inducing activity and tumor-specific cytoxicity	[92]
In vitro	59.2 µg/ml	Jurkat	Berberine induced apoptosis and S phase arrest of cell cycle	[93]
In vitro	NA	K562	Berberine resulted in apoptosis	[94]
In vitro	75 µM/ml	K562	It is suggested that berberine may play its apoptosis-inducing role by reducing survivin levels	[95]
In vitro, *In vivo*	100 µM	Jurkat, U937	Berberine induced apoptosis and autophagy as well as promoting doxorubicin-induced autophagy	[53]
In vitro	100 µM	EU-4 cells	Berberine led to apoptosis which is mediated by XIAP suppression	[54]
In vitro	100 µM	EU-1, EU-4, EU-6, EU-8, Sup-B13, UOC-B1	Berberine induced apoptosis mediated by P53 and MDM2	[55]
In vitro, *In vivo*	50 µM	KOPN-8, EU-4, NALM-6, EU-6, SEM	Berberine induced apoptosis and reduces cell viability through XIAP downregulation	[59]
In vitro, *In vivo*	5 µM	-	Berberine stimulated autophagic degradation of BCR-ABL and BCR-ABL T315I and overcomes imatinib-resistance	[62]
In vitro	50 µg/ml	HL60	Berberine induced apoptosis which is related to downregulation of nucleophosmin/B23 and telomerase activity	[68]
In vitro	15-60 µM	HL-60, murine WEHI-3	Berberine induced G2/M arrest by inhibiting cyclin B1 and promoting Wee1	[70]
In vitro	50 µM	HL-60	Berberine activated capase-3 and caspase-8 leading to apoptosis	[73]
In vitro	60 µM	HL-60, murine WEHI-3	Berberine induced apoptosis through activating caspase-3	[75]
In vitro	40-160 µM	L1210	Berberine inhibited the NAT activity and AF-DNA adduct formation	[77]
In vitro	1.0, 2.5, 4.0 and 5.0 mM	HL60	Berberine-derived Quinolino-benzo-[5, 6]-dihydroisoquindolium compounds are highly selective ligands for G-quadruplex DNA in c-myc oncogene	[96]
In vitro	25-100 µg/ml	L1210	Berberine led to G0/G1 cell cycle arrest and apoptosis	[97]
In vitro	6.25 µM	Jurkat	Berberine had a synergistic effect with TPD7 on cell growth through Ephrin-B2 signaling	[65]
In vivo	200mg/Kg	WEHI-3	Berberine inhibited leukemic cell line	[98]
In vitro	25 µg/ml	HL-60	Berberine induced apoptosis	[99]
In vitro	4 microg/ml	L120	Berberine induced apoptosis	[100]
In vitro	15, 57, 74, 221, 40 and 80 µM/mL (IC50)	K562, U937, P3H, Raji	Berberine and coptisine which are compounds of Coptis chinensis inhibited cell proliferation	[1]
In vitro	100 µM	THP-1	Berberine increased the expression of CDK inhibitors and anti-inflammatory cytokines as well as downregulating CDK2.	[65]
In vitro, *In vivo*	100 µM	EU-6 and SKW-3	Berberine induces autophagic death by inactivating AKT/mTORC1 pathway	[101]
In vitro, *In vivo*	10 µmol/L	K562	Berberine induces autophagic degradation of BCR-ABL T315I and BCR-ABL by recruiting LRSAM1 to overcome imatinib resistance	[102]

and clinical investigations must be conducted to confirm the observed effects *in vitro*.

LIST OF ABBREVIATIONS

ALL = Acute Lymphoblastic Leukemia

CLL = Chronic Lymphoblastic Leukemia

AML = Acute Myeloid Leukemia

CML = Chronic Myeloid Leukemia

ROS = Reactive Oxygen Species

MAPK = Mitogen-activated Protein Kinase

PI3K = Phosphatidyl Inositol-3-Kinase

NF-κB = Nuclear Factor-κB

JAK/STAT = Janus Kinase/signal Transducer and Activator of Transcription

COX-2 = Cyclooxygenase-2

Hsp = Heat Shock Proteins

AhR = Aryl Hydrocarbon Receptor

MDM2 = Mouse Double Minute-2

XIAP = X-linked Inhibitor of Apoptosis Protein

PIM-2 = Proviral Integration of Moloney Virus-2

DAXX	=	Death Domain Associated Protein
BCR-ABL	=	Breakpoint Cluster Region Protein/Abelson Murine Leukemia Viral Oncogene Homolog
AHR	=	Aryl Hydrocarbon Receptor

AUTHORS' CONTRIBUTIONS

JH and MRMF contributed to the conception, design, and drafting of the manuscript. ZA, PMD, MAM, and BY contributed to reviewing relevant literature. All authors approved the final version for submission.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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