



Role of Apoptosis and Mitochondrial Dysfunction in the Treatment of Leukemia Types

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Abstract

Leukemia is a common reason of mortality in worldwide and useful therapeutic strategy is needed in order to its incidence. Induction of apoptosis can inhibit cell proliferation and compounds with this property are required for the treatment of leukemia. Considering the important issue that the rate of proliferation of cancer cells is high, thus mitochondrial dysfunction can abrogate their growth and ultimately reduce blood tumors. In this review study, we focus on compounds with anticancer activity, whose mechanism of their action is induction of apoptosis and mitochondrial dysfunction and also explain their effect on cancer cells. Our review showed that these compounds exhibit potential anti-leukemia activity after incubation in leukemia cell lines. Therefore; they are promising compounds to treat leukemia, however the need to evaluate their effects on normal cells in order to determine their toxicity.

Keywords: Leukemia; Apoptosis; Mitochondria dysfunction; Proliferation

Introduction

Given that existing treatments, hematologic disorders still are most frequent of cancers and their mortality rate is very high caused by drug resistant [1]. Leukemia is defined as high growth of blood-forming cells caused by cell death failure and abrogation of cells differentiate of hematopoietic cells [2,3]. Although these events occur in white blood cells but other blood cells are involved in other types of leukemia, generally this type of cancer divided to two subtypes including: acute (fast growing) or chronic (slow growing) [4]. According to study national cancer institute, annually 7.1 per 100,000 person death due to cancer in the USA [5]. Leukemia is one of the main reason mortality either developed or developing countries thus it burdens high expenditure to health field [6]. It has been estimated that approximately 50% young adult patients and 90% older patients death due to Acute Myeloid Leukemia (AML) or Acute Lymphoid Leukemia (ALL), respectively [7,8]. Apoptosis is a promising way to abrogate cancer cell, this process trigger through two pathways, intrinsic pathway by cytochrome c releasing from mitochondria to cytosol and subsequently activation of caspase, while extrinsic pathway starts after caspase-8 activation through binding of pro-apoptotic ligand to death receptor [9]. Interestingly, pro-apoptotic protein Bax, Bak ratio and anti-apoptotic protein Bcl-2 and Bcl-xl are other important molecular to induce apoptosis [10,11]. Mitochondria have pivotal role in oxidative metabolism and apoptosis and it has been reported that to target mitochondria can be a promising strategy for treatment of cancer [12]. In addition, given that leukemia cells without p53 have potential ability to maintain respiratory function due to increment of compensatory in mitochondrial biogenesis [13]. Therefore, mitochondrial dysfunction is a key strategy to induce apoptosis in leukemia cells [14]. Given that high costs related to treatment of patients with leukemia [15], therefore there is dire need to treatments with low cost and without any side effect to overcome leukemia. Here, we reviewed compound with anticancer activity against leukemia cancer through induction of apoptosis and its relevant events.

Review Method

At first, we search papers with topic of leukemia treatment by induction of apoptosis and mitochondria dysfunction using keywords such as leukemia and apoptosis, leukemia cell line and apoptosis, human leukemia and apoptosis, leukemia cell line and mitochondria dysfunction from

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Received Date: 19 Dec 2017

Accepted Date: 31 Jan 2018

Published Date: 08 Feb 2018

Citation:

Hassanpour SH, Dehghani MA, Karami
SZ, Dehghani F. Role of Apoptosis
and Mitochondrial Dysfunction in the
Treatment of Leukemia Types. *Ann
Blood Cancer*. 2018; 1(1): 1002.

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Table 1: Effect of anti-apoptotic treatment against leukemia.

Compound	Cell line	Finding(s)	References
MPT0B169 (tubulin inhibitor)	HL60 and NB4 cell lines	Anticancer activity against nonresistant or multidrug resistant types of AML	[16]
Miltirone	HL-60 and Jurkat cell lines	Apoptosis induction, mitochondrial dysfunction and trigger of ER stress	[17]
18 α -glycyrrhetic acid	HL-60 cell line	induction of extrinsic and intrinsic apoptotic pathways	[18]
Celastrol	t(8;21) AML cell lines Kasumi-1 and SKNO	Apoptosis induction, mitochondrial dysfunction	[19]
CCY-1a-E2	HL-60, K562, KG-1 and KG-1a	Reduction of cell proliferation, apoptosis induction, DNA fragmentation and mitochondrial dysfunction	[20]
5'-Cl	HL-60 cell line	Induction apoptosis and mitochondrial dysfunction	[21]
MG132	U937 leukemia cell lines	Improvement of doxorubicin anticancer effect by abrogation of senescence, p65 phosphorylation as well as DOX-induced Bcl-2 anti-apoptotic protein	[22]
FK866	CLL cells from patients	reduction of NAD and ATP, increase of ROS formation and apoptosis induction	[23]
Fuoidan	U937 cell line	To have apoptotic effect and activation of p38 mitogen-activated protein kinase	[24]
Quinazolinone MJ-29	Murine myelomonocytic leukemia WEHI-3 cell line	To have apoptotic effect, ER stress induction, reduction of cancer complication in leukemic mice	[25]
UCN-01 and MEK inhibitors	U937 monocytic leukemia cell line	Cell growth inhibition, mitochondrial dysfunction and induction of apoptosis	[26]
KP372-1	AML cell line	Inhibition of PI3K/AKT and FLT3, ROS increase, mitochondrial dysfunction, caspase activation and externalization of phosphatidylserine	[27]
Sodium selenite	NB4 cell line	Induction of mitochondrial apoptotic pathways and endoplasmic reticulum stress	[28]
α -mangostin	HL60 cell line	Caspases activation, mitochondria dysfunction, cytochrome c/AIF releasing, increase of ROS	[29]
MS-275	Human leukemia and lymphoma cell lines (U937, HL-60, K562, and Jurkat), primary acute myelogenous leukemia blasts	Obvious anti-proliferative effect, promotion of differentiation, apoptosis induction, anti-apoptotic proteins level reduction, mitochondrial dysfunction, increase of ROS level	[30]
Suberoylanilide hydroxamic acid	U937, HL-60 and Jurkat cell lines	Apoptosis induction, mitochondrial dysfunction	[31]
Arsenic	K562 and HL-60/Bcr-Abl cell lines	To have apoptotic effect	[32]
ABT-737	Acute myeloid leukemia blast	Inhibition of cancer cells survival	[33]
Cladribine	JM1, Jurkat and U937 cell lines	Induction of apoptosis, mitochondrial dysfunction	[34]

ER: Endoplasmic Reticulum; NAD: Nicotinamide Adenine Dinucleotide; ATP: Adenosine Triphosphate; PI3K/AKT: Phosphoinositol-3-kinase /Protein Kinase B; FLT3: Fms-Like Tyrosine Kinase 3

2000 to now. Then the papers were fully read and their findings written. The results were summarized in (Table 1).

The Effect of Apoptosis Induction and Mitochondrial Dysfunction in Leukemia Treatment

As shown in (Table 1), following compounds have anticancer activity due to induction of apoptosis. Here, we describe how their anticancer activity.

1. It has been revealed that MPT0B169 as a tubulin inhibitor has apoptotic effects against nonresistant AML cell line (HL60 and NB4 cells) as well as MDR1-mediated taxol-resistant AML cells by DNA fragmentation, induction of disturbance of loss of mitochondrial membrane potential, cytochrome c releasing into cytosol, cleavage and activation of caspase-9 and caspase-3 and poly (ADP ribose) polymerase cleavage. In addition, it had an inhibitory effect on Mcl-1 level as an antiapoptotic protein. Therefore, this study showed that MPT0B169 acts as an anticancer drug against either nonresistant or multidrug resistant types of AML [16].

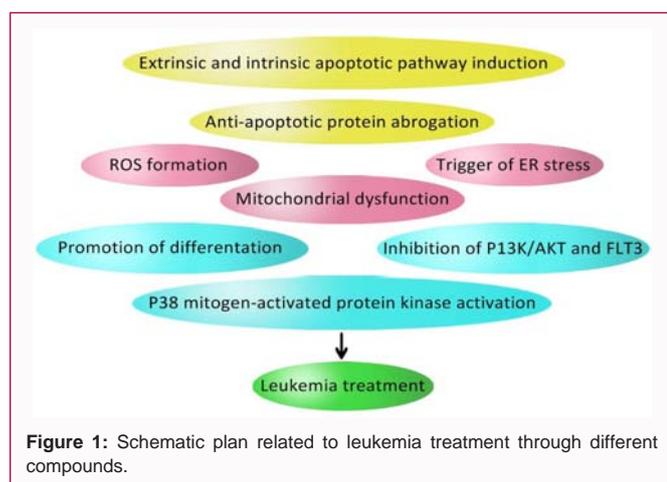
2. Miltirone probably acts as an anti-leukemic drug, because incubation of human leukemia cell lines (HL-60 and Jurkat cells) with miltirone leads to apoptosis induction through collapses of mitochondria membrane potential (MMP), increase of Bax/Bcl-2 ratio, and cytochrome c releasing. Miltirone also is a main trigger of Endoplasmic Reticulum (ER) stress by effect on unfolded protein

(phosphorylated PERK, eIF2 α , GRP78, GRP94, and caspase-12). Moreover, it has potential effect in efflux Ca²⁺ from the ER stores and increase of loading mitochondrial Ca²⁺ in cytosol. Reduction of complex III activity and induction of Reactive Oxygen Species (ROS) formation are other effects in cancer cells [17].

3. During treatment of human leukemia HL-60 cells by 18 α -glycyrrhetic acid occurs apoptosis that leads to inhibition of cell proliferation. Evaluation of mechanism showed that 18 α -glycyrrhetic acid results in reduction of mitochondria membrane potential ($\Delta\Psi_m$) and increase of caspase-8, caspase-9 and caspase-3 activities, releasing of cytochrome c and AIF from mitochondria, increment of levels of pro-apoptotic proteins (Bax and Bid), reduction of anti-apoptotic proteins (Bcl-2 and Bcl-xl). Interestingly it led to increase Fas and Fas-L due to interaction with death receptor in HL-60 cell line. Indeed, 18 α -glycyrrhetic acid is a anticancer drug through either induction of extrinsic or intrinsic apoptotic pathways [18].

4. Evaluation of celastrol against leukemia confirmed that it is a useful drug to treat Acute Myeloid Leukemia (AML) due to its effect on activation of caspases and disturbance of mitochondrial function in t(8;21) AML cell lines Kasumi-1 and SKNO. Other anticancer effects of celastrol were down-regulation of AML1-ETO fusion protein and C-KIT kinases, inhibition of AKT, STAT3 and Erk1/2. Indeed, it becomes to a promising drug for patients with AML [19].

5. Determination of molecular mechanism related to anticancer



activity of CCY-1a-E2 (2-[(3-methoxybenzyl) oxy] benzaldehyde) multiple leukemia cell lines (HL 60, K562, KG 1 and KG 1a) against revealed that it leads to arresting of G2/M phase and up-regulation of cyclin B, CyclinDependent Kinase 1 (CDK1), cell division cycle 25C (cdc25C) and p21 protein expression. CCY-1a-E2 induced apoptosis by increase of activation of caspase-8, caspase-9 and caspase-3, increase of Fas/CD95, Bax, Bcl 2 and cleaved PARP, releasing of cytochrome c. In addition, DNA fragmentation and mitochondrial dysfunction through 4',6 diamidino 2 phenylindole (DAPI) staining and disruption of mitochondrial membrane potential, respectively were confirmed [20].

6. Compound of [(E)-1-(5'-Chloro-2'-oxoindolin-3'-ylidene)-6-ethyl-2, 3, 6, 9-tetrahydro-2, 9-dioxo-1H-pyrrolo [3, 2-f] quinoline-8-carboxylic acid] or 5'-Cl is a potential apoptotic drug against HL-60 cell line. Indeed, incubation of this cell line with 5'-Cl results in increase of Reactive Oxygen Species (ROS) formation, depolarization of the mitochondrial inner membrane, reduction of ATP level in cell, modulation of expression and phosphorylation of Bcl-2 and Bax and releasing of cytochrome c to cytosol as well as induction of activation of caspases. Therefore, it is a prominent apoptosis inducer [21]. Doxorubicin (DOX) is considered as a prominent anticancer drug but it also activates the nuclear factor kappa B (NF- κ B) pathway that results in increase of tumor cell survival.

7. Use of MG132 can be a good solution in order to efficacy enhancement of doxorubicin through reduction of senescence, p65 phosphorylation as well as DOX-induced Bcl-2 anti-apoptotic protein that ultimately leads to inhibition of cell proliferation and induction of apoptosis in U937 leukemia cell lines [22].

8. In order to solve a treatment for chronic lymphocytic leukemia (CLL), a research group was incubated CLL cells from patients with FK866 (nicotinamidephosphoribosyltransferase inhibitor). The results showed that it results in depletion of cellular NAD, reduction of ATP, increase of ROS formation as well as apoptosis induction [23].

9. Fucoidan is a sulfated polysaccharide related to marine algae with anticancer drug because increase of caspases activation, Bid cleavage, influx pro-apoptotic Bax into the mitochondria, cytochrome c releasing from mitochondria to cytosol and disturbance of mitochondria membrane potential occur subsequently incubation of U937 cell line with fucoidan. In addition, activation of p38 mitogen-activated protein kinase (MAPK) was key effect of fucoidan to reduce

leukemia cancer cells [24].

10. Based on finding obtained from treatment of murine myelomonocytic leukemia WEHI-3 cell line with quinazolinone MJ-29, it has been revealed that this compound is a novel anticancer drug against leukemia due to cell viability reduction, induction of apoptosis intrinsic pathway and also increment of releasing of intracellular Ca^{2+} and Endoplasmic reticulum stress. Moreover, it increased levels of calpain 1, CHOP and p-eIF2 α pathways in this cell line. During in vivo study was revealed that it has obvious effects to reduce complication of leukemia in leukemic mice by enhancement of total survival rate and body weight as well as inhibition of spleen and liver enlargement [25].

11. Incubation of U937 monocytic leukemia cell line with UCN-01 and MEK inhibitors as a new strategy for treatment of leukemia leads to cell cycle arresting, mitochondrial dysfunction and induction of apoptosis [26].

12. Given that aberrant activation of phosphoinositol-3-kinase (PI3K)/protein kinase B (AKT) and Fms-like tyrosine kinase 3 (FLT3) signaling occur during acute myelogenous leukemia (AML) and as it has pivotal role in leukemia cell survival and resistance to chemotherapy, therefore their inhibition by KP372-1 (novel multiple kinase inhibitor) can be a promising way for treatment of leukemia. Indeed, this inhibitor leads to inhibition of AKT, PDK1, and FLT3, reduction of phosphorylation of AKT on both Ser473 and Thr308, abrogation of phosphorylation of p70S6 kinase, BAD, and Foxo3a via PI3K/AKT signaling and down-regulation of PIM-1. Interestingly, increase of ROS generation, mitochondrial dysfunction, activation of caspase and externalization of phosphatidylserine were observed after incubation AML cell line with KP372-1 [27].

13. Treatment of human acute promyelocytic leukemia NB4 cell line with sodium selenite results in ROS level increase, disturbance of mitochondrial membrane potential, caspases activation and induction of endoplasmic reticulum stress. This study indicated anticancer activity of sodium selenite against leukemia [28].

14. α -mangostin (a xanthone obtained from mangosteen pericarps) has apoptotic effect after its incubation to HL60 cell line. Detection of mechanism showed that it leads to activation of caspase-9 and caspase-3. Other anti-leukemic effects of α -mangostin were loss of mitochondria membrane potential, reduction of intracellular ATP level, increase of ROS formation, and releasing of cytochrome c/AIF [29].

15. In a study, it has been reported that MS-275 (histone deacetylase inhibitor) results in inhibition of p21CIP1/WAF1-mediated growth, increment of CD11b expression (differentiation markers) and hypo phosphorylated retinoblastoma protein and down-regulation of cell cycle-related proteins including cyclin D1 after its incubation in human leukemia and lymphoma cell lines (U937, HL-60, K562, and Jurkat) and primary acute myelogenous leukemia blasts. Interestingly, it had apoptotic effect at higher dose and led to increase of reactive oxygen species formation, loss of mitochondrial membrane potential and releasing of cytochrome c into cytosol. In addition, it reduced protein levels of Mcl-1 and XIAP (anti-apoptotic proteins) [30].

16. Evaluation of anticancer activity of SAHA (Suberoylanilidehydroxamic acid), histone deacetylase inhibitor, on myelomonocytic leukemia cell line (U937) showed that it leads to

increase of procaspase-3 and -8 cleavage, activation of Bid, diminish of $\Delta\Psi$, and cytochrome c releasing. The parallel results also showed in other leukemic cells (HL-60 and Jurkat) [31].

17. Moreover, it has been revealed that arsenic results in cytochrome c releasing, loss of inner membrane potential, caspases activation, generation of reactive oxygen species. These event reduced cell viability in K562 and HL-60/Bcr-Abl cells (contain p210 and p185 Bcr-Abl, respectively) and HL-60 cell types (HL-60/Bcl-2, HL-60/Bcl-x_L and HL-60/VCR) with over expression of Bcl-2, Bcl-x_L, MDR and MRP proteins respectively [32].

18. In a study was confirmed that ABT-737 (a small-molecule BH3 mimetic) has anti-cancer activity against acute myeloid leukemia blast so that it leads to increase of disruption of the BCL-2/BAX complex and BAK-dependent [33].

19. Treatment of JM1, Jurkat and U937 cell lines with cladribine (2-chloro-2'-deoxyadenosine) confirmed anti-leukemic effect of cladribine because it induced mitochondrial transmembrane potential loss, caspase activation (caspases 3, 6, 8 and 9) and developed typical apoptotic morphology [34].

Conclusion

High rate of cell growth in types of leukemia as other types of cancer are showed and inhibition of cell proliferation is a necessary proceeding to reduce cancer cells and this event need to occur before formation of malignancy. Cell death by induction of apoptosis is a useful strategy to diminish tumor whether intrinsic or extrinsic pathway. As shown in (Figure 1), our review revealed that apoptosis induction is main mechanism of leukemia cell lines abrogation after incubation with above compounds. This process was related to mitochondria dysfunction by loss of mitochondria membrane potential and releasing of cytochrome c into cytosol. In addition, abrogation of anti-apoptotic protein is other way to induce apoptosis by above compounds. Probably, oxidant property of above compound is most important reason to explain their anticancer activity but activation of p38 mitogen-activated protein kinase, inhibition of PI3K/AKT and FLT3, promotion of differentiation are other reasons reduction of cancer cells. Finally, we suggest that evaluate the effects of their compounds on normal cells in order to level of their toxicity in further studies.

Declarations

Acknowledgements

Us acknowledgements and gratefulness at the beginning and at last is to god who gave us the gift of the mind. The authors thank Young Researchers and Elite Club, Yasooj Branch, Islamic Azad University due to cooperation in this study.

Conflict of interest statement

The authors declare that there is no conflict of interest regarding this study.

Financial support and sponsorship

This study was supported by the authors named in this article.

Contribution of authors

This work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article was borne by the authors named in this article.

Ethical approval

This research does not contain any studies with human participants or animals and was performed by the authors alone.

References

1. Stankovic T, Marston E. Molecular mechanisms involved in chemoresistance in paediatric acute lymphoblastic leukaemia. *Srp Arh Celok Lek.* 2008;136(3-4):187-92.
2. Petrie K, Zelent A, Waxman S. Differentiation therapy of acute myeloid leukemia: past, present and future. *Curr Opin Hematol.* 2009;16:84-91.
3. Pal K. Cell growth inhibition and apoptosis by extract of basella alba plant on U937 cells. *World J Pharmacy Pharm Sci.* 2016;5:1251-61.
4. Kamba PT, Kamdje AHN. Signaling pathways in leukemia: any role for medicinal plants in leukemia therapy. *J Dis Med Pla.* 2015;1(5):76-9.
5. Cronin K, Ries L, Edwards B. The Surveillance, Epidemiology, and End Results (SEER) Program of the national cancer institute. *Cancer.* 2014;120:3755-3757.
6. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. *CA Cancer J Clin.* 2015;65(1):5-29.
7. Döhner H, Estey E, Grimwade D, Amadori S, Appelbaum FR, Büchner T, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. *Blood.* 2017;129(4):424-47.
8. Harrison CJ, Johansson B. Acute lymphoblastic leukemia, in *Cancer Cytogenetics: Chromosomal and Molecular Genetic Aberrations of Tumor Cells.* In: Heim S, Mitelman F (eds.). 4th edn. 2015.
9. Burmistrova O, Perdomo J, Simões MF, Rijo P, Quintana J, Estévez F. The abietane diterpenoid parvifloron D from *Plectranthus ecklonii* is a potent apoptotic inducer in human leukemia cells. *Phytomedicine.* 2015;22(11):1009-16.
10. Brunelle JK, Letai A. Control of mitochondrial apoptosis by the Bcl-2 family. *J Cell Sci.* 2009;122(Pt-4):437-41.
11. Nascimento PS, Ornellas AA, Campos M, Scheiner M, Fiedler W, Alves G. Bax and bcl-2 imbalance and HPB infection in penile tumors and adjacent tissues. *Prog Urol.* 2004;14(3):353-9.
12. Modica-Napolitano JS, Singh K. Mitochondria as targets for detection and treatment of cancer. *Expert Rev Mol Med.* 2002;4(9):1-19.
13. Ogasawara MA, Liu J, Pelicano H, Hammoudi N, Croce CM, Keating MJ, et al. Alterations of mitochondrial biogenesis in chronic lymphocytic leukemia cells with loss of p53. *Mitochondrion.* 2016;31:33-9.
14. Tofolean IT, Ganea C, Ionescu D, Filippi A, Garaiman A, Goicea A, et al. Cellular determinants involving mitochondrial dysfunction, oxidative stress and apoptosis correlate with the synergic cytotoxicity of epigallocatechin-3-gallate and menadione in human leukemia Jurkat T cells. *Pharmacol Res.* 2016;103:300-17.
15. Warkentin AA, Lopez MS, Lasater EA, Lin K, He BL, Leung AY, et al. Overcoming myelosuppression due to synthetic lethal toxicity for FLT3-targeted acute myeloid leukemia therapy. *Elife.* 2014;22:3.
16. Wang CC, Liu HE, Lee YL, Huang YW, Chen YJ, Liou JP, et al. MPT0B169, a novel tubulin inhibitor, induces apoptosis in taxol-resistant acute myeloid leukemia cells through mitochondrial dysfunction and Mcl-1 downregulation. *Tumor Biol.* 2016;37(5):6065-72.
17. Zhou L, Jiang L, Xu M, Liu Q, Gao N, Li P, et al. Miltirone exhibits antileukemic activity by ROS-mediated endoplasmic reticulum stress and mitochondrial dysfunction pathways. *Sci Rep.* 2016;6:20585.
18. Huang YC, Kuo CL, Lu KW, Lin JJ, Yang JL, Wu RS, et al. 18 α -glycyrrhetic acid induces apoptosis of HL-60 human leukemia cells through caspases-and mitochondria-dependent signaling pathways. *Molecules.*

- 2016;21(7):E872.
19. Yu X, Ruan X, Zhang J, Zhao Q. Celastrol Induces Cell Apoptosis and Inhibits the Expression of the AML1-ETO/C-KIT Oncoprotein in t (8; 21) Leukemia. *Molecules*. 2016;21(5). pii:E574.
 20. Lin CF, Yang JS, Lin C, Tsai FJ, Lu CC, Lee MR. CCY-1a-E2 induces G2/M phase arrest and apoptotic cell death in HL-60 leukemia cells through cyclin-dependent kinase 1 signaling and the mitochondria-dependent caspase pathway. *Oncol Rep*. 2016;36(3):1633-9.
 21. Saleh AM, Aljada A, El-Abadelah MM, Sabri SS, Zahra JA, Nasr A, et al. The Pyridone-Annelated Isoindigo (5'-Cl) Induces Apoptosis, Dysregulation of Mitochondria and Formation of ROS in Leukemic HL-60 Cells. *Cell Physiol Biochem*. 2015;35(5):1958-74.
 22. Ortiz-Lazareno PC, Bravo-Cuellar A, Lerma-Díaz JM, Jave-Suárez LF, Aguilar-Lemarroy A, Domínguez-Rodríguez JR, et al. Sensitization of U937 leukemia cells to doxorubicin by the MG132 proteasome inhibitor induces an increase in apoptosis by suppressing NF-kappa B and mitochondrial membrane potential loss. *Cancer cell Int*. 2014.
 23. Gehrke I, Bouchard ED, Beiggi S, Poepl AG, Johnston JB, Gibson SB, et al. On-target effect of FK866, a nicotinamide phosphoribosyl transferase inhibitor, by apoptosis-mediated death in chronic lymphocytic leukemia cells. *Clin Cancer Res*. 2014;20(18):4861-72.
 24. Park HS, Hwang HJ, Kim GY, Cha HJ, Kim WJ, Kim ND, et al. Induction of apoptosis by fucoidan in human leukemia U937 cells through activation of p38 MAPK and modulation of Bcl-2 family. *Mar Drugs*. 2013;11(7):2347-64.
 25. Lu CC, Yang JS, Chiang JH, Hour MJ, Lin KL, Lin JJ, et al. Novel quinazolinone MJ-29 triggers endoplasmic reticulum stress and intrinsic apoptosis in murine leukemia WEHI-3 cells and inhibits leukemic mice. *PLoS One*. 2012;7(5):e36831.
 26. Dai Y, Yu C, Singh V, Tang L, Wang Z, McInistry R, et al. Pharmacological inhibitors of the mitogen-activated protein kinase (MAPK) kinase/MAPK cascade interact synergistically with UCN-01 to induce mitochondrial dysfunction and apoptosis in human leukemia cells. *Cancer Res*. 2001;61(13):5106-15.
 27. Zeng Z, Samudio IJ, Zhang W, Estrov Z, Pelicano H, Harris D, et al. Simultaneous inhibition of PDK1/AKT and Fms-like tyrosine kinase 3 signaling by a small-molecule KP372-1 induces mitochondrial dysfunction and apoptosis in acute myelogenous leukemia. *Cancer Res*. 2006;66(7):3737-46.
 28. Guan L, Han B, Li Z, Hua F, Huang F, Wei W, et al. Sodium selenite induces apoptosis by ROS-mediated endoplasmic reticulum stress and mitochondrial dysfunction in human acute promyelocytic leukemia NB4 cells. *Apoptosis*. 2009;14(2):218-25.
 29. Matsumoto K, Akao Y, Yi H, Ohguchi K, Ito T, Tanaka T, et al. Preferential target is mitochondria in α -mangostin-induced apoptosis in human leukemia HL60 cells. *Bioorgan Med Chem*. 2004;12(22):5799-806.
 30. Rosato RR, Almenara JA, Grant S. The histone deacetylase inhibitor MS-275 promotes differentiation or apoptosis in human leukemia cells through a process regulated by generation of reactive oxygen species and induction of p21CIP1/WAF1 1. *Cancer Res*. 2003;63(13):3637-45.
 31. Almenara J, Rosato R, Grant S. Synergistic induction of mitochondrial damage and apoptosis in human leukemia cells by flavopiridol and the histone deacetylase inhibitor suberoylanilide hydroxamic acid (SAHA). *Leukemia*. 2002;16(7):1331-43.
 32. Perkins C, Kim CN, Fang G, Bhalla KN. Arsenic induces apoptosis of multidrug-resistant human myeloid leukemia cells that express Bcr-Abl or overexpress MDR, MRP, Bcl-2, or Bcl-x_L. *Blood*. 2000;95(3):1014-22.
 33. Konopleva M, Contractor R, Tsao T, Samudio I, Ruvolo PP, Kitada S, et al. Mechanisms of apoptosis sensitivity and resistance to the BH3 mimetic ABT-737 in acute myeloid leukemia. *Cancer cell*. 2006;10(5):375-88.
 34. Marzo I, Pérez-Galán P, Giraldo P, Rubio-Félix D, Alberto A, Naval J. Cladribine induces apoptosis in human leukaemia cells by caspase-dependent and-independent pathways acting on mitochondria. *Biochem J*. 2001;359(Pt 3):537-46.