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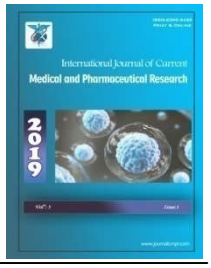

CURCUMIN PLAYS A DUAL ROLE: IN ADJUVANT THERAPY AND REVERSAL OF DRUG RESISTANCE IN ACUTE MYELOGENOUS LEUKEMIA

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ABSTRACT

Cytarabine(cyt) is the drug of choice in treatment of acute myeloid leukemia(AML). Various tumor markers like cytokines (TNF-α, interleukins like IL-6, IL-8, IL-10), transcription factors like NF-κB and their downstream signalling pathways are aberrantly expressed in this form of leukemia. Cytarabine acts by modulating these proteins. However, cytarabine poses several harmful effects and development of drug resistance is a common phenomenon, which negatively affects therapeutic outcome. During drug resistance, the above-mentioned proteins are further deregulated. Cytarabine resistance is characterized by high expression of multi-drug resistant proteins p-glycoprotein and MRP. To overcome the adverse effects of cytarabine, non-toxic means is preferred for a better result. This study aimed to tackle these problems using phytochemical curcumin. HL-60 cells were exposed to increasing doses of cyt and a drug resistant cell HL-60R was developed, which was found to be resistant to other drugs used in AML therapy. Cyt regulates the aberrant expressions of markers and induces apoptosis in HL-60 cells; the modulation gets enhanced in presence of curcumin. In HL-60R, cyt hardly showed any effect; however, when curcumin was administered to cells in combination with cyt, the tumor markers were found to be modulated by cyt, thus rendering the resistant cells sensitive to the drug. The results obtained highlight the potential of curcumin in enhancing the efficacy of cyt and overcoming drug resistance in AML. Thus, this study shows that curcumin may effectively be used as an adjuvant therapy in AML, though intense clinical studies are warranted in this regard.

INTRODUCTION

Myeloid leukemia, affecting the myeloid tissues, may be classified as chronic or acute depending on its rate of progression. Acute myeloid leukemia (AML) is the most common and lethal forms of acute leukemia in adults [1]. This form of malignancy results due to accumulation of poorly differentiated myeloid cells in the bone marrow and peripheral blood [2]. Chromosomal aberrations in genes that are involved in proliferation and differentiation of hematopoietic cells lead to development of AML [3]. Apart from these, various proteins are aberrantly expressed in AML. Transcription factors like Nuclear Factor-κB (NFκB) and its associated pathways are highly implicated in this form of leukemia. Deregulation of cytokines also may contribute to this malignancy [4]. Tumor Necrosis Factor alpha (TNF-α) is a pro-inflammatory cytokine that is highly expressed in AML and has been reported to induce proliferation of leukemic blast cells [5]. TNF-α activates NFκB, which translocates to the nucleus and regulates the expression of proteins that are involved in leukemogenesis [6]. Other pro-inflammatory cytokines like IL-6 and IL-8 get activated [7]. Anti-inflammatory cytokines like IL-10 is also modulated by NFκB [8]. Aberrant modulation of these markers further cause abnormalities in downstream signalling pathways like Janus kinase-Signal Transducer and Activator of Transcription (JAK-STAT), Mitogen-activated protein kinase (MAPK), 'AKT' Phosphoinositide 3-kinase [9]. IL-6 binds to its receptor to activate the JAK-STAT pathway, which is highly expressed in myeloid leukemia [10]. MAP kinases are serine threonine kinases that mediate neoplastic transformation and progression of cell cycle and are regulated by TNF-α [11]. Abnormal modulation of the PI3K/Akt pathway is implicated in the etiology of AML [12]. Cross-talk between these signalling pathways also plays pivotal role in leukemogenesis. Despite rapid advances in therapeutic modalities, AML still remains one of the difficult cancers to treat and prognosis of the disease is poor [13]. This disease is mainly incident in the elderly population who are often unable to tolerate the treatment regimens. Thus overall survival rate for AML is still very low [14]. Chemotherapy is the main therapeutic modality in AML. The most commonly

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used chemotherapeutic drug is cytarabine, which acts by interfering with DNA synthesis. Cytosine gets metabolized into cytosine arabinoside triphosphate intracellularly which causes DNA damage in the S phase [15]. Though considered as one of the most effective drugs in treatment of AML, it poses various undesirable side effects on the patient. Apart from adverse effects, development of drug resistance is another common hindrance in AML therapy. In order to overcome these problems and to improve prognosis, natural nontoxic remedy may be a respite. Natural compounds are bestowed with anti-cancer properties [16]. The popular Indian spice curcumin, extracted from *Curcuma longa* shows anti-leukemia properties and is known to revert drug resistance in a variety of cancers [17]. Curcumin is also free from toxicity as it differentially targets the cancer cells sparing the normal ones [18]. Thus the potential of curcumin to revert drug resistance in AML needs to be explored.

Present study has been conducted on a human acute acute promyelocytic line HL-60 and its drug resistant counterpart HL-60^R. This study aims to elucidate whether curcumin can reverse cytarabine resistance in AML cells. This study may also highlight the potential of curcumin as a chemo-enhancer in acute myeloid leukemia.

MATERIALS AND METHODS

Materials

Cell culture media RPMI-1640 was obtained from GIBCO-BRL India Pvt. Ltd, New Delhi, India. Acrylamide, N, N'-methylenebisacrylamide, Fetal Bovine Serum (FBS) and ELISA kits were purchased from Invitrogen BioServices India Pvt. Ltd., Bangalore, India. Bovine serum albumin (BSA), Ponceau S, 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES), CHAPS, dithiothreitol (DTT), RNase A, proteinase K, ethylene glycol-O,-O'-bis,(2-aminoethyl) N,N,N',N'-tetra acetic acid (EGTA), propidium iodide (PI), curcumin and IM were procured from Sigma, MO, USA. Nitrocellulose membrane was obtained from Hybond ECL, Amersham Biosciences, UK. Tris, 5-bromo-4-chloro-3-indolyl phosphate/nitro blue tetrazolium (BCIP-NBT), glycine, and sodium dodecyl sulfate (SDS) were purchased from Amresco, Ohio, USA. Goat anti-rabbit IgG-alkaline phosphatase conjugate was obtained from Abcam. Assay kits for assessing activities of caspases 3, 8 and 9 were procured from Millipore, Billerica, MA. Antibodies against IL-6, TNF-α (Biorbyt); IL-8, NF-κB (p50 and p65 subunits) and IL-10, cytochrome c, Bcl-2, Bax, Apaf1 (Abcam); p38 Map Kinase, Ras, Raf, PI3K, Akt, JAK2, STAT3, Pgp, MRP1 (Genetex) were used for western blotting. Other reagents were purchased locally and were of analytical grade.

Methods

Cell Culture

Acute promyelocytic cells of human origin, HL-60 was procured from National Centre for Cell Science (NCCS), Pune. They were maintained in RPMI-1640 supplemented with 10% heat inactivated FBS and antibiotics. Cells were maintained in a humidified atmosphere of 5% CO_2/95% air at 37˚C.

Isolation of Lymphocytes

Heparinized blood was collected from healthy individuals, layered on Histopaque and subsequently centrifuged to obtain a buffy coat [19]. This coat is rich in peripheral blood lymphocytes. The isolated lymphocytes were maintained in an incubator at 37˚C containing a humidified atmosphere of 5% CO_2.

Development of Drug Resistance in AML cells.

Logarithmically growing HL-60 cells were exposed to gradually increasing concentrations of cytarabine, starting from 0.1 nM. The cells, named as HL-60^R, were isolated at 1000 nM cytarabine and were maintained in presence of same concentration of drug.

Treatment Protocol

Exponentially growing HL-60 and HL-60^R cells were treated with increasing doses of cytarabine (0.1, 1, 10 and 100 μM) alone and in presence of Curcumin (30 μM) for 24 hours.

Cell Cytotoxicity Assay

MTT assay was used to determine the cytotoxicity of cytarabine to HL-60 and Hl-60^R cells [20]. Cytotoxicity of resistant cells to adriamycin, another common drug used in AML therapy was assessed to verify cross-resistance.

Determination of Levels of Cytokines by Enzyme-linked Immunosorbent assay

The levels of cytokines TNF-α, IL-6, IL-8, and IL-10 were detected in AML cells by quantitative sandwich ELISA using respective kits as per manufacturers protocol [19].

Assessment of Activity of NF-κB (p65)

NF-κB activity was assessed using a kit using nuclear extracts as per laboratory protocol [21].

Western Blotting Analysis

Western blot (WB) technique was employed to assess the expressions of Pgp, MRP1, NF-κB (p50 and p65 subunits), JAK2, STAT3, p38 Map kinase, Ras, Raf, PI3K, AKT, cytochrome c, Bcl-2, Bax, Apaf1 in HL-60 and Hl-60^R cells using corresponding antibodies, following protocol of Sarkar et al [21].

Assessment of Caspase Activity

Cell lysates were used to assess the activities of caspases 3, 8 and 9 following manufacturer's protocol [19].

Assessment of Apoptosis

PI Staining

Cells were treated as per protocol described before, harvested, washed, stained with (50μg/ml) propidium iodide solution and incubated in dark for 10 min. The cells were then mounted on glass slides and visualized under a fluorescence microscope for determination of apoptotic cells.

TUNEL assay

Apoptosis was confirmed using in situ Apoptosis Detection Kit following laboratory protocol [22] . Cells were fixed with a solution of paraformaldehyde/PBS (pH7.4). Methanol in 0.3% H_2O_2 was used to remove endogenous peroxidises. This step was followed by addition of permeabilization buffer. Apoptotic cells were labelled with fluorescein-dUTP followed by addition of Anti-FITC HRP Conjugate and incubated. DAB was then added to the cells. The cells were further counterstained with methyl green and viewed under light microscope.

Assessment of Cytochrome c Release

Detection of release of cytochrome c was done by fractionating treated cells into mitochondrial and cytoplasmic fractions as per laboratory protocol [20]. Proteins were estimated from both fractions and subjected to western blot analysis as described previously.

Statistical Analysis

Statistical analysis was performed using SPSS 10.0 software (one way ANOVA followed by Dunett t-test).

RESULTS

Development of Drug Resistance and its Validation

Constitutive levels of multi drug resistant proteins Pgp and MRP1 were assessed in both HL-60 and HL-60^R cells by western blot analysis. Expression of these proteins was found to be negligible in HL-60 cells; whereas in the resistant cells, these proteins were seen to be expressed at very high levels (Figure1A). This observation confirmed development of drug resistance in AML cells. During course of development of drug resistance, the levels of these proteins increased with increasing doses of cytarabine (Figure1B). GSH levels were however found to remain the same during development of resistance as revealed in Figure1B. This shows that GSH pathway is not responsible for development of drug resistance in this particular case. Increased expression of Pgp and MRP1 was found to be appreciably reduced by 30µM Curcumin (Figure 1C). Cytotoxicity of drugs used in AML therapy to HL-60^R cells was studied using MTT assay. Results indicate that the developed resistance is not only to cytarabine but also to adriamycin (Figure 1D).

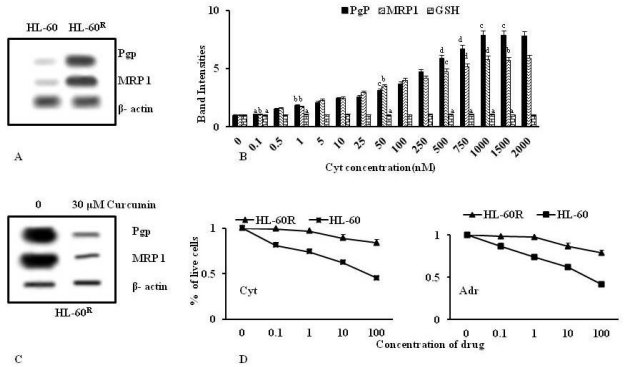

Figure 1

Figure 1

A. Expressions of multi-drug resistant proteins Pgp and MRP1 were observed in parental HL60 and drug resistant cells HL60^R by Western Blotting technique. The expressions of these proteins were found to be higher in resistant cells as compared to drug sensitive parental cells, thus confirming development of drug resistance. β-actin was used as the loading control. **B**. Band intensities were calculated from western blot bands and it was observed that in HL60^R, expression of Pgp and MRP1 increases with dose of cytarabine (cyt) upto 1000 nm. Beyond this concentration, the expressions remain nearly the same. Hence the resistant cells were isolated at 1000 nm cyt. GSH levels were found to remain unchanged. The values are mean of three independent experiments ± SE and are significant with respect to control HL60 cells. {a($p<0.05$), b($p<0.01$), c($p<0.005$), d($p<0.0005$)}. **C**. Expressions of Pgp and MRP1 were down-regulated by 30 µM curcumin in resistant cells as revealed by western blotting. **D**. MTT assay was carried out to assess whether the developed HL60^R cells show cross-resistance to other drugs used in AML therapy like adriamycin. Results depict that HL60^R is resistant not only to cyt but also to adriamycin.

Curcumin Reversed the Developed Drug Resistance

It was intended to study whether curcumin reverses resistance to cytarabine in HL-60^R cells. HL-60 and HL-60^R cells were exposed to increasing concentrations of cytarabine and curcumin, alone or in conjuction, for 24 hours. It has been reported previously that curcumin increases the cytotoxicity of cytarabine to HL-60 cells [20]. Cytarabine itself hardly shows any toxicity to HL-60^R cells. Presence of curcumin along with the drug renders the cells sensitive to the treatment as shown in Figure 2. Concentration of cytarabine corresponding to 50 % cell killing i.e. the EC_{50} values were calculated in absence and presence of curcumin. The values are tabulated in Table 1. EC_{50} of cytarabine in HL-60^R was >> 100 µM in absence of curcumin, indicating drug resistance. Presence of curcumin along with the drug brought down the EC_{50} value to 64.54 µM.

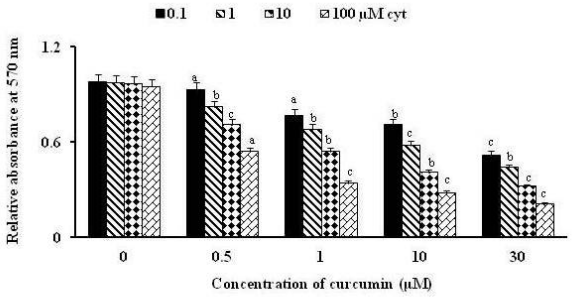

Figure 2

Figure 2

Developed HL60^R shows resistance to cyt upto a concentration of 100µM as revealed by MTT assay results. The cells get sensitized to the drug in presence of curcumin. experiments have been repeated thrice and the results are significant a($p<0.05$), b($p<0.005$), c($p<0.0005$) with respect to cells treated only with the drug cytarabine.

Table 1 EC_{50} of cytarabine gets diminished in resistant HL60 cells when curcumin is administered to cells along with the drug.

Cell	Drug	Compound	EC_{50} (µM)
		Cur-	>>100
HL60^R	Cyt	Cur+	64.54

Modulation of Markers by Cytarabine in AML cells, as Influenced by Curcumin

HL-60 and HL-60^R cells were treated with increasing doses of cytarabine (0, 0.1, 1, 10, 100 µM) for 24 h, in absence and presence of 30 µM Curcumin. ELISA results reveal that pro-inflammatory cytokines TNF-α, IL-6, IL-8 were down-regulated and anti-inflammatory cytokine IL-10 was up-regulated by cytarabine in HL-60 cells; the extent of modulation was much more pronounced when curcumin was present with the drug. In HL-60^R cells, cytarabine itself did not show much modulation on these markers; however, when

curcumin was present, the markers were found to be greatly modulated. The results are depicted in Figure 3.

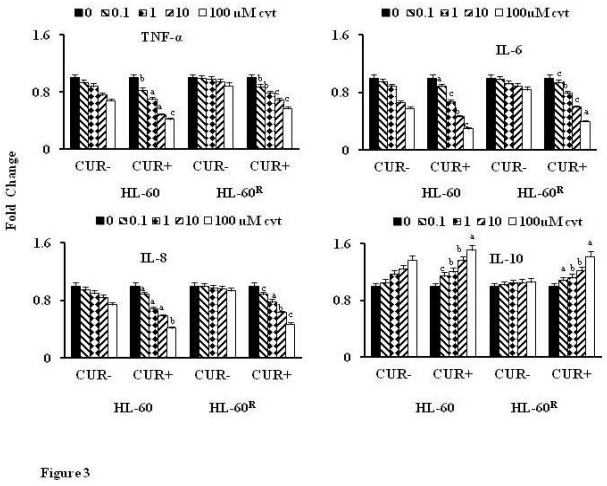

Figure 3

Figure 3

ELISA was used to assess levels of cytokines (TNF-α, IL-6, IL-8 and IL-10) in HL60 and HL60^R cells. The bar diagrams denote modulation of these cytokines by cyt alone and in combination with 30μM Curcumin. The values represent average of three independent experiments and are significant a($p<0.05$), b($p<0.005$) and c($p<0.0005$) with respect to only cyt treated cells. In presence of 30μM curcumin, the cytokines were found to be modulated in both the cell lines.

NF-κB is a transcription factor that is intricately associated with the development and progression of acute leukemias and it also contributes to development of drug resistance. Therefore, modulation of NF-κB is also of much relevance in cancer research. Thus, it is worthwhile to see whether the combination of cytarabine and curcumin could influence levels of NF-κB in parental and resistant cell lines. It was observed that NF-κB expression (Figure 4A) and activity (Figure 4B) are brought down by the combinatorial therapy not only in HL-60 but also in HL-60^R. TBP was used as the loading control as depicted in Figure 4A.

Expressions of JAK2, STAT3, p38 Map kinase, Ras, Raf, PI3K, AKT were assessed by western blot technique in both HL-60 and HL-60^R cells. All these proteins are over-expressed in HL-60 cells compared to normal lymphocytes and are even higher in HL-60^R cells (Figure 4C). Cytarabine brings down the expression of these proteins (extent may be different) in HL-60 cells but not in the resistant cells. When the resistant cells are treated with curcumin along with the drug, these proteins get down-regulated. The representative western blot bands are shown in Figure 4D.

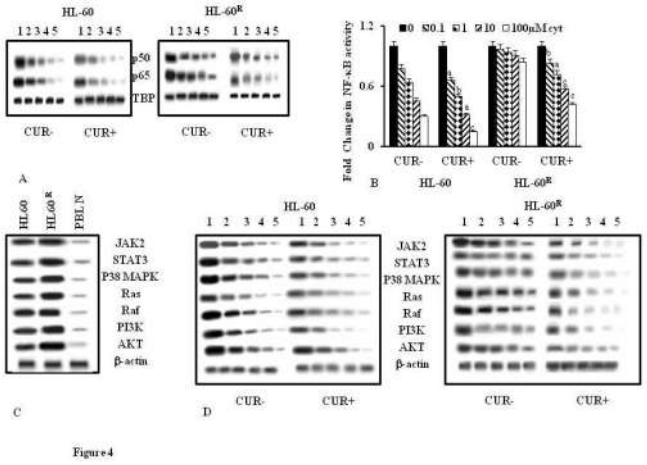

Figure 4

Figure 4

Expression of NFκB subunits (p50 and p65) were assessed by western blotting in HL60 and HL60^R cells. **A.** Figure denotes modulation of these markers by cytarabine alone and in conjunction with 30μM curcumin. **B**. Activity of NFκB was studied using a kit. Inhibitory effect of cyt on NFκB activity was enhanced by 30μM curcumin not only in HL60 but also in HL60^R cells. Values are significant a($p<0.05$), b($p<0.005$) and c($p<0.0005$) with respect to cells treated with drug only and are mean of three independent experiments ± SE . **C**. Constitutive expression of JAK2, STAT3, p38 Map kinase, Ras, Raf, PI3K, AKT in HL60, HL60^R cells and control lymphocytes isolated from normal healthy donors (PBL-N) were studied by western blotting. These markers are highly expressed in HL60 cells as compared to PBL-N and are even higher in resistant cells. **D**. Modulation of above mentioned myeloid leukemia markers by cyt alone and with 30μM curcumin in HL60 and HL60^R cells as studied by western blot analysis. Curcumin increases the modulatory efficacy of cyt in both drug sensitive and drug resistant AML cells. Lanes 1, 2, 3, 4, 5 denote the expressions of proteins at 0, 0.1, 1, 10, 100 μM cytarabine respectively in absence and presence of curcumin in HL60 and HL60^R cells.

Induction of Programmed Cell Death by cyt, as Influenced by Curcumin

Induction of apoptosis was studied by staining the cells with PI. Induction of apoptosis was more when cells are treated with both cytarabine and curcumin, compared to cytarabine alone, as revealed by fluorescent microscopic examination of HL60 cells. Cytarabine alone failed to induce cell death in resistant cells, but, presence of curcumin renders the cells fragile and imparts sensitivity to the drug. Typical morphological features of apoptosis, like cell shrinkage, chromatin condensation, fragmented nuclei, membrane blebbing and apoptotic bodies were observed as depicted in Figure 5A. TUNEL assay was also employed to ascertain induction of programmed cell death, where apoptotic cells were observed under a light microscope. Representative figures are shown in Figure 5B. Numbers of apoptotic and non-apoptotic cells were counted and the apoptotic index was calculated. It was observed that in both parental and resistant cells, administration of curcumin to cells along with the drug increased the apoptotic index as shown in Figure 5C.

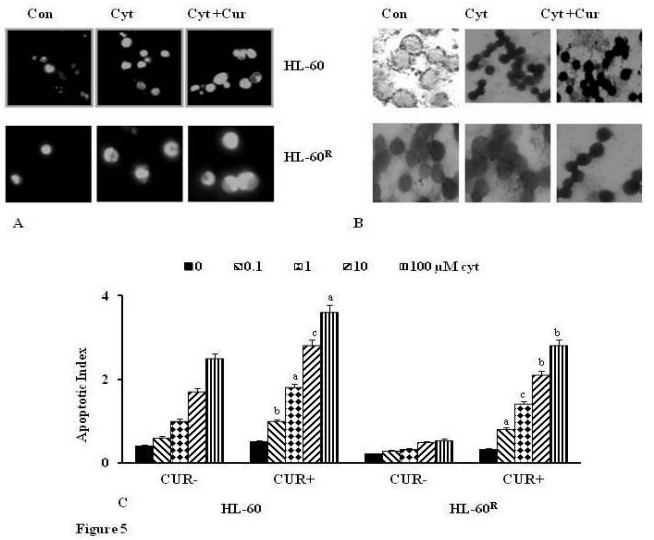

Figure 5

Induction of apoptosis by PI staining [**A**] and TUNEL assay [**B**] has been studied in HL60 and HL60^R cells. Based on these results, apoptotic index was calculated and is depicted in **C**. Findings reveal that cyt induces apoptosis in HL60 cells which is enhanced by30µM curcumin. In HL60^R cells, cyt fails to induce apoptosis, which gets facilitated by the phytochemical. Results are significant a($p<0.05$), b($p<0.005$) and c($p<0.0005$) with respect to cells treated only with cyt.

Activation of Caspases in AML Cells

Caspases, a group of cysteine-dependent aspartate-directed proteases play key roles in apoptosis. Cells were treated with cytarabine in absence and presence of curcumin as described previously and activities of caspases 3, 8 and 9 were assessed. The results are depicted as bar diagram in Figure 6A. Results show that caspases get activated when HL-60 cells are treated with cytarabine; however, the activation is more in presence of curcumin. Cytarabine itself fails to induce activation of caspases in the resistant HL-60 cells. When curcumin is present along with the drug, caspases are found to be activated. Another interesting observation in this regard is that caspase 9 was found to be activated the most, suggesting that the intrinsic pathway of apoptosis may be involved.

Modulation of Markers Involved in Intrinsic Pathway of Apoptosis

The observation that caspase 9 is activated the most, led us to study the modulation of some important makers involved in intrinsic pathway of apoptosis by the combinatorial therapy. Expressions of cytochrome c, Bcl-2, Bax, Apaf1 were studied in AML cells (Figure 6B). Expression of cytochrome c was found to decrease in the mitochondrial fraction whereas its expression increased in the cytoplasmic fraction, thereby suggesting release of cytochrome c from mitochondria, a typical feature of intrinsic pathway of apoptosis. Bcl2 expression was found to decrease, with a concomitant up-regulation of Bax and Apaf1. All these observations confirmed that intrinsic pathway of apoptosis was followed. The results obtained so far was with cytarabine alone, the effects were more pronounced in presence of curcumin. In the resistant cells, cytarabine hardly showed any effect, but the modulation was facilitated when curcumin was administered to the cells along with cytarabine.

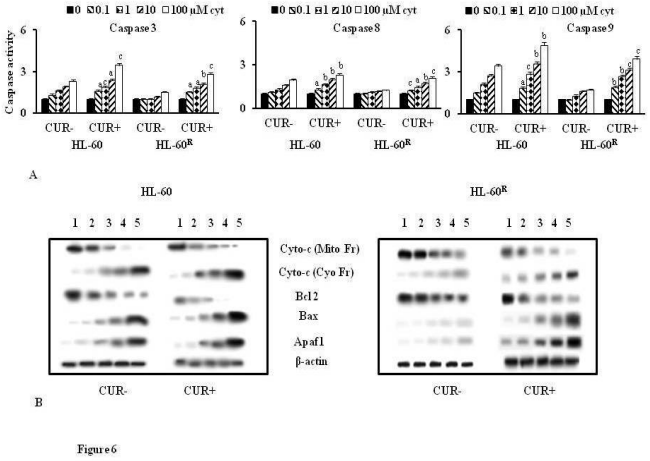

Figure 6

A shows activation of caspases 3, 8 and 9 by cyt alone and in conjunction with 30µM curcumin in HL60 and HL60^R cells. Results show that caspase 9 is more prominently activated, thereby indicating involvement of intrinsic pathway of apoptosis. Values depicted as bar diagrams are mean of three independent experiments ± SE and are significant a($p<0.05$), b($p<0.005$) and c($p<0.0005$) with respect to cyt treated cells. **B**. Expression of proteins involved in the intrinsic pathway have been studied by western blot analysis. Bands obtained confirm that apoptosis was being induced by this pathway and curcumin increases the regulatory effect of cyt on these markers in both HL60 and HL60^R cells. Lanes 1, 2, 3, 4, 5 denote the expressions of proteins at 0, 0.1, 1, 10, 100 µM cytarabine respectively in absence and presence of curcumin in HL60 and HL60^R cells.

The Bax/Bcl2 ratio was calculated and it was found to be much higher when cytarabine and curcumin are used in conjunction (Table 2). These observations suggest that use of curcumin along with cytarabine may induce apoptosis in resistant cells as well. This may aid in overcoming drug resistance, which is in line with our finding (Figure1C), that curcumin may reduce the expression of drug resistance proteins.

Table 2 Modulation of Bax/Bcl 2 ratio by cytarabine, as influenced by curcumin

Cell		Con	Cyt (100µM)	Cyt+Cur
HL60	Bcl 2	1	0.61	0.47
	Bax	1	2.10	2.49
	Bax/Bcl 2	1	3.44	5.3
HL60^R	Bcl 2	1	0.87	0.62
	Bax	1	1.17	2.41
	Bax/Bcl 2	1	1.345	3.89

DISCUSSION

Cytarabine is the first line chemotherapy treatment for patients suffering from acute myeloid leukemia [23]. Cytarabine acts by targeting various protein markers and their associated signalling pathways involved in leukemogenesis. But prognosis of the disease is still not up to the mark. Development of resistance to the drug during therapy poses a major hindrance to achieving a satisfactory clinical outcome [24]. Thus, elucidation of the underlying mechanisms is important. Phytochemicals like curcumin possess a plethora of anti cancer properties and may come to the rescue. They are almost free from side effects as they preferentially target the

cancer cells [25]. They also play a role in reversal of cancer drug resistance. This study aimed to assess the potential of curcumin in reverting drug resistance in AML. HL-60^R cells were developed from parental cells by exposing the exponentially growing cells to gradually increasing concentrations of cytarabine. Drug resistance development was confirmed by studying the elevated expression of multi drug resistant proteins Pgp and MRP1, which was diminished by curcumin. The resistant cells isolated were resistant not only to cytarabine but also to adriamycin, another drug commonly used in AML therapy. Results reveal that curcumin not only increases the cytotoxicity of HL-60 cells towards cytarabine [20] but also lowers the level of resistance in HL-60^R cells, thereby rendering the cells sensitive to cytarabine.

Several biomarkers like pro- inflammatory cytokines (TNF-α, IL-6, IL-8), anti- inflammatory interleukin IL-10, transcription factors like NFκB and their downstream signalling proteins contribute to leukemogenesis leading to abnormal proliferation and evasion of apoptosis. Cytarabine modulated the expression of these markers in HL-60 cells; the extent of regulation was pronounced in presence of curcumin. The leukemic biomarkers mentioned before are even higher in resistant leukemic cells, imparting hindrance to treatment methods. The drug alone hardly caused any modulation of these proteins in the resistant cells. Treatment of cells with a combination of cytarabine and curcumin results in modulation of these markers, thereby making the cells sensitive to the drug. Chemotherapeutic drugs mostly work by inducing apoptosis in cancer cells. The combinatorial treatment protocol could induce apoptosis in both drug sensitive parental cells and drug resistant cells as revealed by microscopic examination of typical apoptotic morphological features (PI staining) and DNA fragmentation (TUNEL assay). Induction of programmed cell death involves various key proteins like caspases. Cytarabine treatment resulted in caspase activation in HL-60 cells but failed to do so in the resistant ones. However, a combinatorial treatment of curcumin and the drug, could induce caspase activation in the resistant cells as well. Results also reveal that activation of caspases 3 & 9 are more than caspase 8, indicating that intrinsic pathway of apoptosis is mainly responsible for death of leukemia cells. Release of cytochrome c from mitochondria and modulation of Apaf1, Bid, Bax, Bcl-2 by cytarabine and curcumin further support the findings.

The present study sheds light on the potential of dietary phytochemical curcumin in tackling the problem of cytarabine resistance in acute myeloid leukemia when used in combination with the drug. Further research is warranted to establish the role of this bio-molecule in combinatorial therapeutic regimen in leukemia. Therefore, curcumin may be considered as an effective modality in leukemia control.

CONCLUSION

Despite advances in therapy of acute myeloid leukemia, prognosis of the disease is poor. Cytarabine is commonly used in therapy but this drug poses severe adverse effects on the patient and development of resistance to the drug is quite common. Therefore natural means of tackling AML need to be elucidated. In this study, Indian spice curcumin has been found to be effective as an adjuvant therapy that tackles the severe adverse effects of cytarabine on one hand by reducing drug dose and overcomes drug resistance on the other. Therefore, this bio-molecule could be of help in controlling acute myeloid leukemia.

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