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Short Communication

Ivermectin and dexamethasone combination induces apoptosis in SUP-B15 cell line

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Abstract

The development of glucocorticoid resistance has complicated the management of acute lymphoblastic leukemia (ALL), leading to increased mortality rates. Ivermectin, a low-cost and well-established anthelmintic, exhibits anticancer potential and may enhance glucocorticoid toxicity in ALL, offering a possible strategy to overcome resistance. The aim of this study was to evaluate the apoptotic effect of combining ivermectin with dexamethasone in ALL. ALL SUP-B15 cells were cultured under standard conditions before treatment with dexamethasone (200 nM) alone or combined with ivermectin (5, 10, and 20 µM), with an untreated group serving as the control. Cytotoxicity was assessed using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay by measuring cell viability and inhibition. Apoptosis was evaluated through BAX, BCL-2, and CASP3 gene expression analysis using reverse transcription-polymerase chain reaction (RT-PCR). The findings revealed that the combination of ivermectin and dexamethasone was superior in the repression of ALL cell viability compared to control (p<0.001). The combination of dexamethasone 200 nM + ivermectin 20 µM demonstrated the most significant cell inhibition of 38.16±0.04% (p<0.001) and produced the lowest cell viability of 61.84±0.05% (p<0.001). Moreover, the combination of dexamethasone 200 nM + ivermectin 20 µM demonstrated superior upregulations of *BAX* (p<0.001) and *CASP3* (p<0.001). In conclusion, the addition of ivermectin (5 µM) to dexamethasone regimen (200 nM) increases its cytotoxic and apoptotic activities against SUP-B15 cell line as observed by the *CASP3* and *BAX* upregulation. Studies to confirm the enhanced anticancer activity by this combination by observing the protein levels and animal studies are warranted.

Keywords: Acute lymphoblastic leukemia, apoptosis, dexamethasone, glucocorticoid resistance, ivermectin

Introduction

Acute lymphoblastic leukemia (ALL) is a cancer of the lymphoid cells characterized by their immaturity. It disrupts bone marrow production, including platelets, erythrocytes, and leukocytes [1]. Children under 15 years old are most likely to suffer from ALL, with the highest occurrence at 2–5 years [2]. In 2019–2020, more than 400,000 new leukemia cases and more than 300,000 leukemia deaths were reported [3,4]. However, ALL is acknowledged as the first curable cancer. The child survival rate has risen dramatically from less than 10% in 1960 to 90% in 2015 [5]. High relapse-free survival rates are also reported, with 97.9%, 91.3%, and 86.3% at 1,

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3, and 5 years old, respectively [6]. Notably, ALL survival rates and overall prognosis are determined by the treatment [7]. Chemotherapy is currently the primary ALL treatment, aiming to cure leukemia by inducing remission, intensification, and maintenance [2,5]. The regimen used includes multiple cytostatic drugs, of which glucocorticoids are currently considered the most potent to hinder growth and promote apoptosis in cancer cells [8,9].

Glucocorticoids primarily affect the lymphoid tissue by halting cell growth and triggering apoptosis [10]. Initially discovered in 1944, hydroxyl corticosterone triggers apoptosis in malignant mice cells [10]. Since then, synthesized glucocorticoid has been used in the clinical management of lymphoma and leukemia [10]. Glucocorticoids, particularly prednisone and dexamethasone, remain the principal treatment used in most lymphoid neoplasms in children and adults [11]. Glucocorticoids have been reported to effectively treat ALL due to their cytotoxic effects [11]. However, the development of resistance to glucocorticoids in vivo was reported as an adverse prognostic factor in ALL since it resulted in inadequate response to the treatment [12,13]. As a consequence, the risk of recurrence increases and higher doses of chemotherapy may be needed, potentially leading to severe adverse effects [8,9].

Numerous studies have sought to identify alternative therapeutic approaches to overcome glucocorticoid resistance [14]. A previous study had reported the benefit of dasatinib and glucocorticoid combination in glucocorticoid-resistant ALL [15]. Although the efficacy of the combination was favorable, the cost burden of dasatinib has become a limitation to this combination [16]. The use of cannabinoids was also reported to be beneficial in pediatric ALL [17]. However, the serious side effects including neuronal disruptions leading to cognitive impairment should be considered when administered in pediatric patients [18]. Due to the limitations of the reported alternative for glucocorticoid-resistant ALL treatment, further research is necessary to identify alternative medications with minimum side effects and cost-effectiveness, including the investigation on ivermectin. Ivermectin is widely used as an antiparasite with reported efficacy and safety, even in young children [19], and it has also been identified as having anticancer properties [20,21]. Ivermectin was reported to specifically trigger mitochondrial malfunction and oxidative stress, causing increased apoptosis of leukemia cells, particularly in acute and chronic myeloid leukemia [22,23]. Ivermectin was also found to induce apoptosis and suppress cell growth in a leukemia xenograft model by increasing the cleavage of poly ADP-ribose polymerase (PARP) and caspases [24]. Another study also reported the effectiveness of ivermectin in inducing apoptosis of esophageal carcinoma cells by increasing the ratio of Bcl-2-associated X protein (BAX)/B-cell lymphoma 2 (BCL-2) [25].

The combination of dexamethasone and ivermectin is a promising alternative therapy for leukemia [22,23,26]. Ivermectin and dexamethasone have also been documented to exhibit synergistic effects in managing coronavirus disease 2019 [27]. The aim of this study was to evaluate the role of ivermectin combined with dexamethasone in inducing apoptosis in ALL. The ability of the combinatorial therapy in inducing the apoptosis could be observed by determining the expressions of *BAX, BCL2,* and *CASP3* genes which encode BAX, BCL-2, and caspase-3 proteins, respectively [28].

Methods

Study design and setting

This study was an in vitro experimental study with a post-test-only control group design. The study was conducted in July 2024 at the Primate Animal Study Center, Institute for Research and Community Service, Bogor Agricultural Institute (PSSP LPPM – IPB), Indonesia. Cytotoxic and apoptotic effects of ivermectin and dexamethasone combination was observed on SUP-B15 cell culture. Gene expressions of *BAX, BCL-2*, and *CASP3* were further evaluated using reverse transcription-polymerase chain reaction (RT-PCR).

Cell cultures

Considering the availability of cell lines in the research laboratory, we utilized SUP-B15 cell lines to represent pediatric ALL cells. SUP-B15 cells (ATCC, Manasas, USA) were cultured in RPMI 1640 medium supplemented with 2 mM L-glutamine, 10% heat-inactivated fetal calf serum

(GIBCO, Berlin, Germany), 50 ug/mL streptomycin, and 50 ug/mL penicillin in an incubator at 37°C and 5% CO_2 concentration. The culture process was carried out in 24-well plates at a density of 0.5–2×10^6 cells/mL and incubated for 24 hours. Cell culture was successful when the cells were in the range of 1.5–3×10^6/mL.

Measurement of cytotoxicity activity

Measurement of cytotoxicity activity was carried out on SUP-B15 cells by assessing optical density, cell inhibition, and cell viability. The measurement was assessed using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. This study was conducted following a standard protocol to regulate confounding factors affecting cell viability, including cell density per well and duration of incubation period [29]. SUP-B15 cells were plated in 96-well plates at a density of 2×10^4 cells/well and incubated at 37°C under 5% CO_2 for 24 hours. The cells were categorized into 4 experimental groups: (1) combinations of dexamethasone 200 nM and ivermectin 5 µM; (2) combinations of dexamethasone 200 nM and ivermectin 10 µM; (3) combinations of dexamethasone 200 nM and ivermectin 20 µM; (4) Negative controls. The doses of ivermectin, 5 µM, 10 µM, and 20 µM, were selected based on findings from a prior study that indicated these concentrations triggered apoptosis in leukemia cells [18]. The dose of dexamethasone 200 nM was selected based on a previous report that indicated this concentration to induce *BAX* expressions and inhibit *BCL-2* expressions in leukemia cells [30]. Negative controls were obtained by excluding treatment from the wells. After 72 hours of sample treatment, the MTT assay was conducted by administering 10 µL of MTT (5 mg/mL) to each well. Ethanol 70% was added to solubilize the formazan crystals, the duration of solubilization was about 30 minutes. After 4 hours of incubation at 37°C, measurement of the absorbance value was carried out on a NanoDrop 2000 UV-vis spectrophotometer (Thermo Fischer Scientific, Massachusetts, USA) at a wavelength of 595 nm.

Measurement of *BAX*, *BCL2*, and *CASP3* expressions

Ribonucleic acid (RNA) extraction SUP-B15 cells were added to 6-well tissue culture plates at a density of 10^4 cells/well in triplicate, and incubated for 24 hours under conditions of 95% O_2, 5% CO_2, and 37°C. Upon achieving around 50% confluence, samples were treated with combinations of dexamethasone (200 nM) and ivermectin (5, 10, and 20 µM), while negative controls were obtained by excluding treatment from the wells. The cells were cultured for 48 hours, after which viable cells were collected using 0.125% trypsin. Cells were stained with 0.1% trypan blue, and the viable cell count was determined using a hemocytometer (Neubauer hemocytometer, Germany). The viable cell population was subsequently removed to isolate messenger ribonucleic acid (mRNA). mRNA extraction was conducted utilizing the RNeasy Kit (Qiagen, Düsseldorf, Germany) adhering to the manufacturer's protocols, which vary according to the test. The concentration of extracted mRNA was determined utilizing a NanoDrop 2000 UV-vis spectrophotometer (Thermo Fischer Scientific, Massachusetts, USA).

Gene expressions analysis

The mRNA expression of each gene was quantified using a reverse transcription-polymerase chain reaction (RT-PCR) apparatus IQ5 Multicolor Real-Time PCR Detection System (Bio-Rad). Each reaction comprised 2.5 µL of RNA template, 1 µL of primers for each gene, 12.5 µL of 2× SYBR Green RT-PCR reaction mix, 0.5 µL of iScript One-Step RT-PCR, and 2.5 µL of nuclease-free water. The reaction proceeded under the following conditions: 50°C for 10 minutes to activate reverse transcriptase, followed by 95°C for 5 minutes to inactivate reverse transcriptase. The reaction was conducted for 40 cycles at 95°C for 10 seconds for DNA denaturation, 52°C for 20 seconds for primer annealing, and 72°C for 10 seconds for DNA extension. The baseline and threshold are automatically established by the RT-PCR machine software. The expression of each gene was relatively quantified by ΔΔCt value. All target genes were normalized relative to Glyceraldehyde 3-phosphate dehydrogenase (GAPDH)/beta-actin. The forward and reverse primer sequences of GAPDH/beta-actin were CGG ATITGG TCG TATTGG and TCA AGG TGT GAG GAC TGG, respectively. The forward and reverse primer sequences of *BAX* were CCC GAG AGG TCT TTI TCC GAG and CCA GCC CAT GAT GGT TCT GAT, respectively. The forward and reverse primer sequences of *BCL-2* were GCT CTA AAA TCC ATC CAG and CCT CTC CAT CAT

CAA CTI, respectively. The forward and reverse primer sequences of *CASP3* were ATGGAAGCGAATCAATGGA and TGTACCAGACCGAGATGTC, respectively.

Statistical analysis

Data obtained was analyzed using the IBM SPSS 25.0 software (SPSS Inc., Chicago, United States). The data was subjected to the Shapiro-Wilk normality test. A Levene homogeneity test was performed to determine the data variant. One-way ANOVA was carried out to determine the relationship between the variables tested. The analysis was followed by a Bonferroni post-hoc test. A p-value<0.05 indicated statistical significance.

Results

Cytotoxic effects

The cytotoxicity of dexamethasone-ivermectin combinations on SUP-B15 cells is presented in **Figure 1**. The combination of dexamethasone 200 nM + ivermectin 5 µM yielded a significant inhibitory effect on SUP-B15 cells compared to control (p<0.001). The combination of dexamethasone 200 nM + ivermectin 20 µM had the strongest inhibitory effect (38.16±0.04% (95%CI: 38.06–38.26) and produced the lowest cell viability (61.84±0.05% (95%CI:61.72–61.96)). The combination of dexamethasone 200 nM + ivermectin 20 µM yielded p-values<0.001 when compared to all treatments.

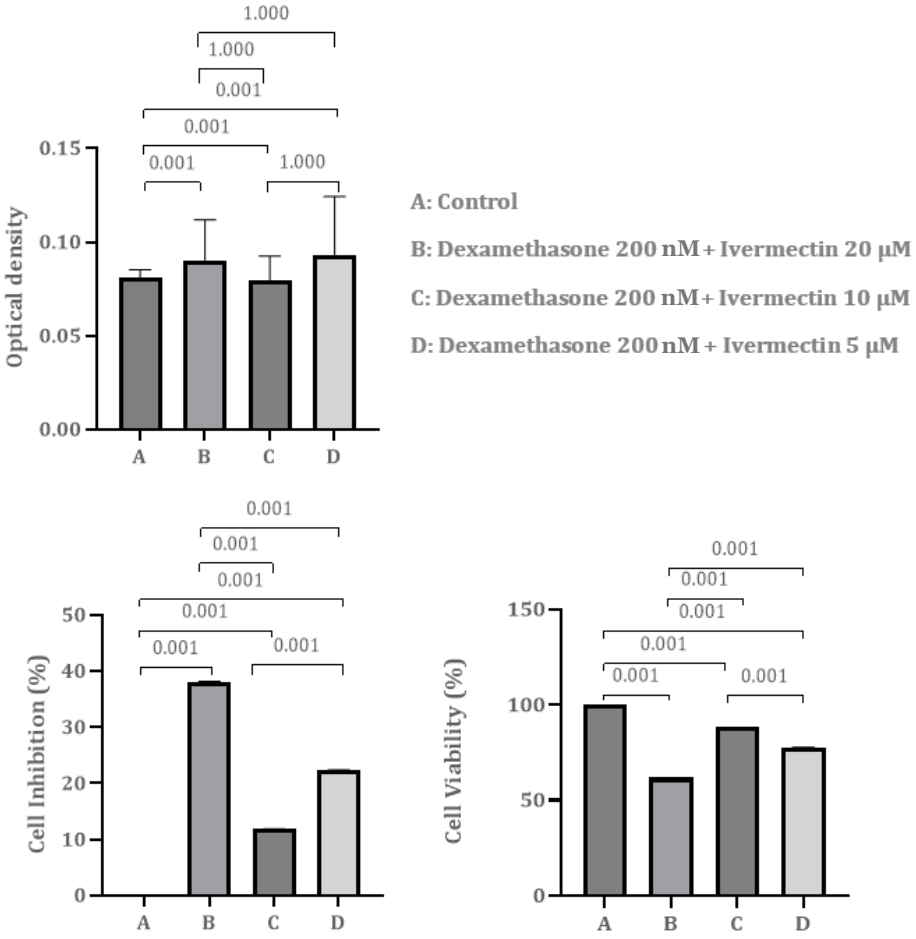

Figure 1. Cytotoxicity activity of combination of ivermectin and dexamethasone on SUP-B15 cells as observed by optical density, cell inhibition, and cell viability.

Apoptotic effects

The relative CT values for *BAX, BCL-2*, and *CASP3* in all groups are presented in **Figure 2**. The combination of dexamethasone 200 nM and ivermectin 20 µM yielded the highest *BAX* and *CASP3* expressions of 31.16±0.15 (95%CI: 30.79–31.53) and 34.74±0.77 (95%CI: 32.82–36.67),

respectively. As compared to control, the combination showed statistical significance of *p*-values of 0.001 and 0.002 for BAX and CASP3 expressions, respectively. On the contrary, the combinations of dexamethasone 200 nM with ivermectin 5 µM or 10 µM significantly downregulated *BAX* and *CASP3* expressions (p=0.001, respectively). As for *BCL-2* expression, statistical significance was only observed in a group treated with dexamethasone 200 nM and ivermectin 20 µM combination (p=0.008), showing an upregulation.

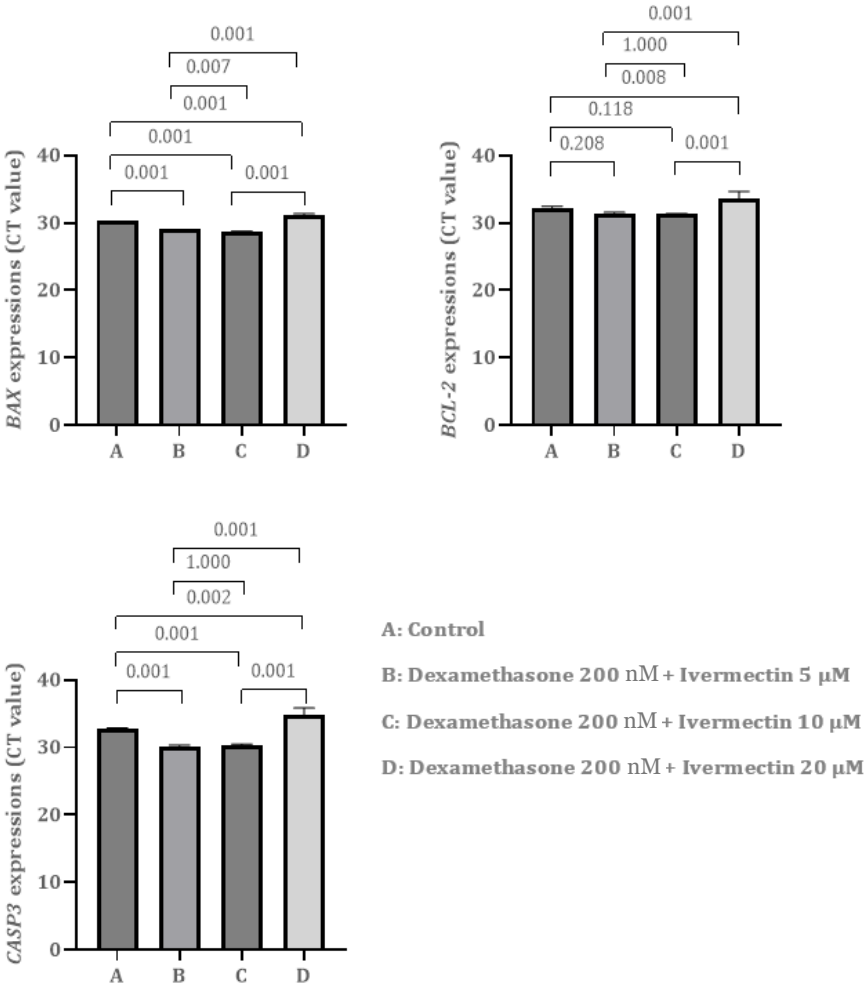

Figure 2. *BAX, BCL2*, and *CASP3* expressions correspond to the administration of dexamethasone and ivermectin combinations.

Discussion

The present study demonstrated that the combination of ivermectin and dexamethasone exhibited cytotoxic effects on SUP-B15 cells in vitro as indicated by the optical density, cell inhibition, and cell viability. The cell inhibition was observed starting from a low-dose combination of dexamethasone 200 nM + ivermectin 5 µM. The finding was consistent with a prior study that demonstrated ivermectin to exhibit cytotoxic effects on colorectal cancer cells starting from a low dose of 5 µM [31]. Ivermectin has been reported to exhibit cytotoxic effects on cancer cells through various mechanisms [32]. Previous studies reported that ivermectin exhibited cytotoxic effects by inducing autophagy and apoptosis [33,34]. Apoptosis was characterized by DNA laddering, distinct morphological alterations, reduced mitochondrial transmembrane potential, phosphatidylserine (PS) exposure, and the activation of caspase-3 [35]. In the present study, the ivermectin and dexamethasone was found to modulate the expression of *CASP3*, indicating the combination plays a role in apoptosis of SUP-B15 cells.

To further understand the apoptosis pathway involved, the expressions of *BAX* and *BCL-2* were evaluated in the present study. We found that ivermectin and dexamethasone upregulated *BAX* expression, yet it also upregulated *BCL-2* expression. The two genes are known to play a key

role in intrinsic apoptotic pathways [36]. This suggested that a combination of ivermectin and dexamethasone involved in the intrinsic apoptotic pathway [37]. This study aligned with the ability of ivermectin to inhibit the proliferation of colorectal cancer cells by upregulating *BAX* [31]. The upregulation of *BCL-2* expression in the present study was contradictory to a previous study reporting the reduction of BCL-2 protein by ivermectin [38]. However, the upregulated *BCL-2* expression does not always reflect the upregulated BCL-2 protein production [39]. A previous study also demonstrated that ivermectin considerably induced reactive oxygen species (ROS) accumulation, suppressed the activation of the nuclear factor kappa B (NF-κB) signaling pathway, and elevated the BAX/BCL-2 ratio, thereby effectively reducing the proliferation of esophageal cancer cells [18]. The upregulation of *BAX* led to the activation of caspase-9 [40]. Activated caspase-9 underwent cleavage, thus triggering the activation of other caspases, including caspase-3 [41]. The activation of caspase-3 triggered mitochondrial malfunction and cell apoptosis [41].

Ivermectin and dexamethasone exhibit a synergistic effect against cancer cells, likely due to their interaction, where concurrent administration reduces drug excretion, leading to increased serum drug concentrations [42,43]. In addition, ivermectin had been noted for its capacity to surmount ALL cell resistance to dexamethasone [32]. An example was the resistance of leukemia cells to dexamethasone, attributed to glucocorticoid receptor phosphorylation and the activation of the AKT pathway and mTOR protein, which could be mitigated by ivermectin via the reduction of AKT and mTOR [23].

One of the limitations in this present study was the use of a single cell line due to cost constraint. The use of single cell line possibly misrepresents the efficacy of ivermectin and dexamethasone combination for ALL, as it missed the variability in each cell line [44]. Study including several cell lines of ALL would provide better evidences and understanding to the role of the ivermectin and dexamethasone combination in ALL. Additional in vivo or clinical trials are suggested to provide better evidence regarding the role of ivermectin and dexamethasone combination in ALL. Another limitation addressed in this present study was the evaluation of apoptotic gene expressions only rather than the apoptotic proteins. Although gene expressions marked protein syntheses, the evaluation of the gene expressions only did not precisely reflect the expressions and activity of the apoptotic protein [39].

Conclusion

The combination of dexamethasone and low-dose ivermectin exhibits cytotoxic and modulatory effects against apoptotic genes such as *BAX* and *CASP3* in SUP-B15 cell lines. Our findings suggested that the combination of dexamethasone and ivermectin could serve as a novel potential anticancer agent for the treatment of ALL, though further studies observing the protein levels remain necessary.

Ethics approval

This study was reviewed and approved by the Research Ethical Committee of the Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia, (clearance number: 665/KEPK/USU/2023) and was conducted according to the Declaration of Helsinki.

Acknowledgments

None.

Competing interests

All the authors declare that there are no conflicts of interest.

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Underlying data

Derived data supporting the findings of this study are available from the corresponding author on request.

Declaration of artificial intelligence use

We hereby confirm that no artificial intelligence (AI) tools or methodologies were utilized at any stage of this study, including during data collection, analysis, visualization, or manuscript preparation. All work presented in this study was conducted manually by the authors without the assistance of AI-based tools or systems.

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