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THE ROLE OF PLANT EXTRACTS IN THE TREATMENT OF LEUKEMIA TYPES

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ABSTRACT: Cancer is one of the most common reasons for mortality worldwide. Leukemia as one type of cancer is a serious threat to human. Although there are many synthetic drugs to treat leukemia, but the use of them is limited due to a side effect, therefore there is a dire need to find a promising solution. Herbs and their compound can be promising candidates for control leukemia. In this study, we review new studies entitled role of extracts of herbs to inhibit leukemia from 2014 to now. Our review study showed that herbs have anticancer activities through cell proliferation inhibition. This feature is due to induction of apoptosis and increase of free radical formation in cancer cell. Finally, we suggest that need to special attention to herbs in order to treat leukemia.

INTRODUCTION: Cancer is considered as the main reason for mortality in developed and developing countries due to changing in lifestyles such as lack of exercise and physical activity, smoking and consuming of fast food [1]. Leukemia as one type of cancer is occurred due to uncontrolled growth of abnormal white blood cells and the inability of blood-forming cells to differentiate into functional white blood cells so that these cancer cell transport to another organ such as lymph nodes, spleen and central nervous system by bloodstream [2, 3]. It can be divided into two types: acute or chronic with fast or slow growing, respectively [4]. Although, the Wnt signaling is considered as a common pathway to induce other hematological malignancies and solids tumors it is one of the pathways involved in leukemia development.

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Also, Notch and SHH pathways have a pivotal role in developing leukemia [4]. In 2012, it was diagnosed about 13,780 new patients with leukemia, interestingly; the mortality related to leukemia was 10,200 in the United States [5]. The National Cancer Institute recently reported that it had been diagnosed 52380 leukemia patients so that 3% of all new cancer cases belonged to leukemia [6]. According to finding obtained from several European CML registries, the annual incidence of chronic myeloid leukemia is 0.7-1.3/ 100,000 [7].

Oxidative stress followed by an imbalance in reactive oxygen species (ROS) formation and inactivity of their scavenging by antioxidant defense systems has a prominent role in cancer pathophysiology [8]. Increase of free radical leads to damage on macromolecule and ultimately increase of malondialdehyde, dityrosine formation, aggregation of protein and DNA fragmentation [9, 10]. Interestingly, it has been observed that ROS induce uncontrolled proliferation due to genetic instability during acute myeloid leukemia [11, 12 13]. In conjunction with the role of oxidative stress in a relapse of acute myeloid leukemia, Zhou *et al*., 2010 conducted a study on 102 patients with acute

myeloid leukemia. The results revealed that levels of advanced oxidation protein products, malondialdehyde and 8-hydroxydeoxyguanosine and adenosine deaminase and xanthine oxidase activities, as well as human thioredoxin (TRX) and indoleamine 2, 3-dioxygenase mRNA levels, were significantly high in relapse status. In contrast, there was not showed reasonable results for parameters such as activities of glutathione peroxidase, monoamine oxidase, and superoxide dismutase as well as level of total antioxidant capacity (T-AOC) [14].

Evaluation of oxidative stress condition in 80 children with acute lymphoblastic leukemia was confirmed higher concentrations of plasmatic thiobarbituric acid reactive substances (TBARS) and serum protein carbonylation in these patients, while they had lower levels of parameters such as activities of whole blood catalase (CAT) and superoxide dismutase (SOD) and concentration of serum Vitamin E. Given that this studies, there is continued oxidative stress in acute lymphoblastic leukemia [13]. The potential ability of cancer cells to produce free radicals particularly O^{2-} is a promising idea to treat cancer because their susceptibility to injury induced by ROS-generating agents is higher than the normal cell. Thus, this strategy is considered as therapeutic selectivity [15].

Today, Use of traditional medicine to design new drugs is a promising idea to treat diseases [16]. Although there are many anticancer drugs, their use is limited due to toxicity, side effect and non-selective targets [17]. Meanwhile, herbs have a pivotal role in promoting health society caused by a high demand by people in worldwide [17]. In association with leukemia, it has been reported that herbs and their bioactive compound were served for treatment of types of leukemia such as CML, AML, lymphoid leukemia and hodgkin's and non-hodgkin's lymphomas [18, 19, 20].

Also, natural products and plant extracts have been investigated for their ability to protect against radiation-induced toxicity [21]. Based on belief of scientists, many compounds identified from plants are considered as anticancer drugs such as quinine, salicylates ergotamine and digitalis. Furthermore, plants are good source from the bioactive substance with an anti-tumor activity that needs to evaluate their ability in this field [4]. Here, we reviewed the role of extracts prepared from plants in the treatment of a type of leukemia.

Review Method: This study aimed to review new studies in association with the effect of extracts prepared from plants to treat leukemia. We collected related studies by searching keywords such as "extract, herb, and leukemia," "extract and herb and apoptosis and leukemia treatment," *etc.* from databases web of science, PubMed and Scopus since 2014 to now. Then, papers were read, and their findings are written.

RESULTS: Given that oil extract obtained from *Argania spinosa* has an anti-proliferative effect against T-cell acute lymphoblastic leukemia human after its treatment into cell lines including JURKAT, MOLT3, and DND41; therefore, it can be a new useful treatment for acute lymphoblastic leukemia. This study was showed that this extract leads to growth inhibition of mentioned cell lines and obvious reduction of mRNA level and activity of ERK1/2 and Notch1 intracellular domain, as proliferation-related proteins [22].

Probably, *Albizia zygia* is a potent anticancer herb because incubation of its aqueous and hydro-ethanolic extracts inhibits cell growth in Jurkat cells. Interestingly, its hydroethanolic extract results in prominent cell morphological changes and increase of DNA fragmentation due to induction of apoptosis in Jurkat cells [23]. It has been suggested that *Moringa oleifera* Lam is a candidate plant to treat leukemia due to inhibition of cell proliferation subsequently its incubation into K562 cell line. They were showed that crude ethanolic extract prepared from *Moringa oleifera* Lam decreases WT1 protein level and has anti-proliferation property [24]. In a study, it has been found that besides inhibition of cell growth in the Jurkat cell line, it had good stability.

Therefore, it could be considered as a promising therapy against leukemia cancer cells [25]. Souid *et al*., 2016 showed that incubation of K562 cells by dehydrated aqueous extract obtained from *Allium roseum* results in inhibition of cell viability (by BCR-ABL kinase dephosphorylation and interference in ERK1/2, Akt, and STAT5 pathways), FOXO3 transcription factor activation

(through Akt kinase inactivation). It also could improve the expression pattern of FOXO3-regulated proapoptotic effectors, Bim and Bax, and cell cycle inhibitor p27 and abrogate vascular endothelial growth factor secretion. Indeed, given that these finding should be special attention to this herb due to its anticancer property [26].

A research group was incubated HL-60 (human promyelocytic leukemia) cell line with aqueous extracts of *Morinda lucida* and *Taraxacum officinale*. The results showed that both extracts is cytotoxic against HL-60 due to proliferation inhibition through reduction of cell viability and apoptosis induction through the increase of DNA fragmentation and changing of cell morphology [27]. Examination on antileukemic effects related to dimethyl sulfoxide extract prepared from *Withania somnifera* was revealed its cytotoxic and genotoxic activity against human T-lymphoblastoid cell line. Indeed, it has been demonstrated that this extract increases intracellular Ca^{2+} accumulation and reactive oxygen species formation as well as induces apoptosis, so that leads to immunogenic cell death (ICD) [28].

Study of the effect of different extracts obtained from *Urtica dioica* on acute myelogenous leukemia was showed that chloroform has strongest effect in reduction of cell viability according to MTT assay on KG-1 cell line. Also, both chloroform and ethyl acetate induced apoptotic pathway based on Flow cytometric analysis. Generally, this study revealed that *Urtica dioica* is a potential therapeutic source to overcome leukemia [29]. Tawil *et al*., 2015 reported that incubation of *Daucus carota* oil extract into several acute myeloid leukemia (AML) cell lines result in apoptosis induction. Interestingly, cytotoxicity related to oil extract was diminished after MAPK pathway inhibition; therefore the anticancer effect of *Daucus carota* is involved in MAPK pathway [30].

A study conducted by Fan *et al*., 2015 confirmed anticancer activity ethanol extract of *Meconopsis horridula* Hook so that it could induce cytotoxicity in L1210 cell line. This effect was through obvious alteration in cell morphology, increase of DNA fragmentation, apoptosis induction and arresting of G2/M related to the cell cycle. Given that this extract had a potential effect of producing reactive oxygen species, thus induction of oxidative stress has a central role in association with the antitumor property of *Meconopsis horridula* Hook [31]. Given that deficiency of apoptosis is main reason resistance to chemotherapy during B cell chronic lymphocytic leukemia (B CLL), Alhosin *et al*., 2015 conducted a study about the apoptotic effect of anthocyanin-rich dietary (*Vaccinium myrtillus*) bilberry extract on B CLL cells obtained from thirty patients. The results indicated that this extract leads to caspase 3 activation and down-regulation of Bcl-2 and UHRF1 (rapid dephosphorylation of Akt and Bad).

Also, it had a prominent effect on the increase of reactive oxygen species level. Moreover, when PEG-catalase was incubated to B CLL cells, the apoptosis induced by extract and its related signaling diminished that confirm the effect of the extract on apoptosis induction in B CLL cells [32]. *Lepidium sativum* is one of the herbs that considered as an antitumor plant because its hydro-alcoholic extract incubation to K562 cells leads to obvious cytotoxic effect based on the evaluation of cell viability by MTT test [33]. For determination of mechanisms related to anti-cancer activity of *Punica granatum* (pomegranate) against K562 cell line (chronic myeloid leukemia (CML) cells) was done a study by Asmaa *et al*., 2015.

According to findings related to this study, this extract leads to either cell cycle arresting or apoptosis induction through inhibition of G2/M phase, increase of p21 and p53 levels and up-regulation of caspases and cytochrome c, respectively [34]. Given that chemotherapy and radiation lead to damage to normal cell during treatment of acute myeloid leukemia; thus they consider as non-selective therapies to overcome leukemia. Also, there is a dire requirement to find a new anticancer drug; for example, *Myrothamnus flabellifolius* could be a promising candidate for this purpose. Indeed, it has been reported that methanol extract of *Myrothamnus flabellifolius* has cytotoxic effect in HL-60 cell line and reduces cell viability by induction of caspase-7 cleavage [35].

Basella alba considers as a natural edible source with antitumor activity so that its methanol extract results in a reduction of cell viability and changing of cell morphology. Also, MTT assay confirmed its

cytotoxic effect against U937 cell line, and it also could induce apoptosis in this cell line [3]. It has well been demonstrated that treatment of HL-60 cell line by ethanol extract prepared from orange (*Citrus aurantium*) leads to cell viability inhibition. Based on WST assay, this extract had cytotoxic activity and based on agarose gel electrophoresis; it was confirmed DNA fragmentation followed by treatment. This study indicated that orange has the potential ability to reduce cancer cell [36].

In 2014, Assadollahi *et al*., suggested that aqueous extract related to *Cinnamon zeylanicum* has a prominent effect in the reduction of human myelocytic leukemia by induction of apoptosis. In other words, they found that incubation of THP-1 cell line with mentioned extract increases Apoptotic cells after determination of Hoechst 33342 staining. Moreover, flow cytometry and MTT assay confirmed cell cycle arresting and inhibition of cell proliferation. Finally, this study introduced a potential anticancer source that needs to perform more investigations in further studies [37].

Investigation of anticancer activity related to *Zanthoxylum heitzii* was confirmed that it has antiproliferative effect in HL-60 cells treated by ethanol extract of *Zanthoxylum heitzii*. This study also revealed that mechanisms related to the antitumor activity of this extract are obvious increase of reactive oxygen species (ROS), disturbance of mitochondrial membrane potential (MMP), DNA fragmentation and cell cycle arrest in G1/G0 phase [38]. Jantova *et al*., 2014 reported that ethanol extract of *Salvia officinalis* has cytotoxic and anti-proliferative properties after its treatment in leukemia L1210 cell line. Interestingly, it induced apoptosis through a pathway related to mitochondrial /caspase [39].

Samet *et al*., 2014 found that ethanol extract of olive (*Olea europaea*) has a potential effect in inhibition of cell growth of K562 cell line. The evaluation of related mechanism was revealed that this extract leads to cells proliferation inhibition, cell cycle arresting (at G0/G1, and then at G2/M phase) and induction of apoptosis. Besides, microarray analysis confirmed high expression of genes related to K562 cells differentiation to monocyte / macrophage lineage (IFI16, EGR1, NFYA, FOXP1, CXCL2, CXCL3, and CXCL8) [40]. In an experiment, it has been indicated that reduction of living cells number, induction of apoptosis occur in Jurkat cell line incubated by ethanol extract of *Convolvulus arvensis*.

Indeed, this study confirms that *Convolvulus arvensis* has potential anti-cancer activity against leukemia cells [41]. Evaluation of the role of n-hexane extract of *Cichorium intybus* in treatment of leukemia confirmed that its treatment is effective in the reduction of cell viability and induction of apoptosis in Jurkat cells as a cell line related to human leukemia [42]. Moreover, it has been shown that reduction of mitochondrial outer membrane permeability and nuclear translocation of apoptosis-inducing factor, induction of LC3-I cleavage result from treatment with leaf extract obtained from *Azadirachta indica*.

TABLE 1: SUMMARIZE OF TREATMENT OF LEUKEMIA BY EXTRACTS OF HERBS

Plant	Extract	Animal model/cell line	Result(s)	References
Argania spinosa	Oil	Three T-ALL cell lines (JURKAT, MOLT3, and DND41)	To have anti-proliferative effects due to inactivation and expression reduction of ERK1/2 and Notch1	22
Albizia zygia	Aqueous and hydroethanolic	JURKAT cell line	To have cytotoxic effects in both extract, apoptosis induction by hydroethanolic extract	23
Moringa oleifera	Ethanolic	K562 cell line	Reduction of WT1 protein	24
Solanum aethiopicum	µEm Labrasol-crude extract	JURKAT cell line	To have an anti-proliferative effect and good stability	25
Allium roseum	Dehydrated aqueous	K562 cell line	Inhibition of cell viability and VEGF secretion, arresting of the cell cycle in molecular level	26
Morinda lucida *Taraxacum officinale*	Aqueous	HL-60 cell line	Reduction of proliferation, induction of apoptosis	27

Withania somnifera	Dimethyl sulfoxide	Human T-lymphoblastoid cell line	Increase of intracellular Ca^{2+} accumulation and ROS level	28
Urtica dioica	Aqueous, hydro-alcoholic, chloroform, ethyl acetate	KG-1 cell line	Chloroform extract; most effective to reduce cell viability, induction of apoptosis by chloroform and ethyl acetate	29
Daucus carota	Oil	AML cell lines (HL60, U937, ML1, ML2, Mono-Mac-1, Mono-Mac-6, KG-1, MV-4-11, TF1-vRaf, TF1-vSrc and TF1-HaRas)	To have apoptotic and cytotoxic effects probably by the MAPK pathway	30
Meconopsis horridula Hook	Ethanol	L1210 cell line	Induction of apoptosis and inhibition of cell cycle by an increase of oxidative stress	31
Vaccinium myrtillus	Anthocyanin-rich dietary extract	B CLL cell obtained from patients	Induction of apoptosis and oxidative stress	32
Lepidium Sativum	Hydro-alcoholic	K562 cell line	To have a cytotoxic effect	33
Punica granatum	Ethanol	K562 cell line	Inhibition of proliferation and induction of apoptosis	34
Myrothamnus flabellifolius	Methanol	HL-60 cell line	To have an apoptotic effect by induction of caspase-7 cleavage	35
Basella alba	Methanol	U937 cell line	Cell viability reduction, cell morphology changing, to have cytotoxic and apoptotic effects	3
Citrus aurantium	Ethanol	HL-60 cell line	Cell viability inhibition, to have cytotoxic activity DNA fragmentation increase	36
Cinnamon zeylanicum	Aqueous	THP-1	induction of apoptosis, anti-proliferative effect, inhibition of cell cycle	37
Zanthoxylum heitzii	Methanol	HL-60 cell line	ROS levels increase, MMP disturbance, DNA fragmentation, and G1/G0 phase arresting	38
Salvia officinalis	Ethanol	L1210 cell line	Cytotoxic activity and reduction of cell proliferation by induction of apoptosis	39
Olea europaea		K562 Cells	Cell cycle arresting, apoptosis induction and K562 cell line differentiation to monocyte/ macrophage lineage	40
Convolvulus arvensis	Ethanol	JURKAT cell line	Cell viability reduction, apoptosis induction	41
Cichorium intybus	n-hexane	JURKAT cell line	Reduction of living cell number and apoptotic activity	42
Azadirachta indica	Extract related to its leaf	PBMC obtained from patients with CLL	Reduction of mitochondrial outer membrane permeability, factors related to apoptosis as well as Bcl-2 and p53 proteins	43
Mentha pulegium	Hydro-alcoholic	K562 cell line	Reduction of cell viability	44
Thymus vulgaris L. *Origanum syriacum* L.	Ethanol	leukemia THP-1 cell line	To have a cytotoxic effect in both extracts, *Thymus vulgaris* L. is safer than *Origanum syriacum* L. due to selective therapeutic activity	45

T-ALL: T-cell acute lymphoblastic leukemia human; VEGF: vascular endothelial growth factor; ROS: reactive oxygen species; AML: acute myeloid leukemia; B CLL: B cell chronic lymphocytic leukemia; MMP: mitochondrial membrane potential; PBMC: peripheral blood mononuclear cell

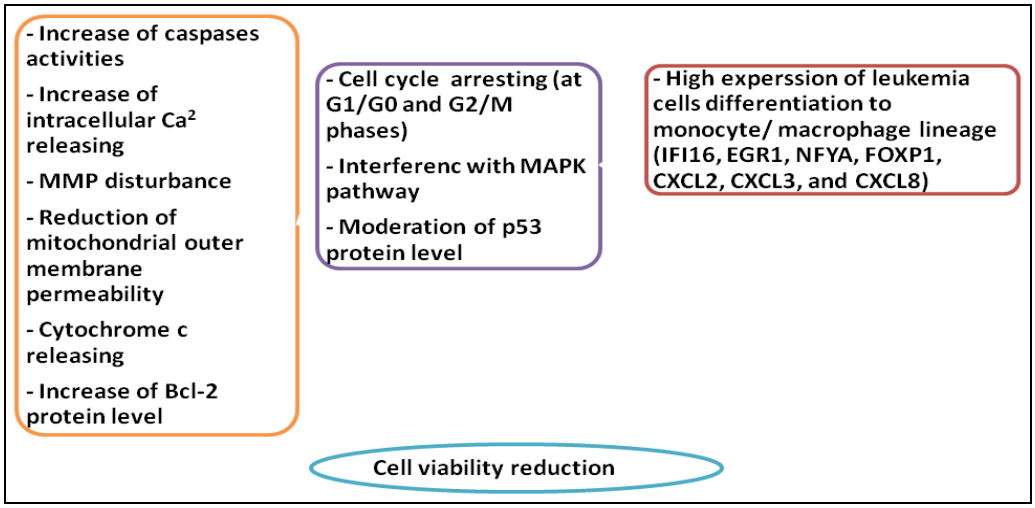

FIG. 1: SCHEMATIC PLAN OF EFFECTS RELATED TO HERBS EXTRACT IN REDUCTION OF CELL VIABILITY

Also, according to biochemical tests, this extract diminished BCl-2 and p53 proteins. Given that anti-tumor activity of this plant, it can be a promising treatment for patients with CLL (B cell chronic lymphocytic leukemia) [43]. To find a useful treatment against chronic myeloid leukemia was evaluated the effect of hydro-alcoholic extract prepared from *Mentha pulegium* on K562 cell line. At the end of the study, it was found promising cytotoxic effect by this extract so that it significantly reduced cell viability [44].

Comparison of effect of two herbs (*Thymus vulgaris* Linn. and *Origanum syriacum* Linn.) against THP-1 leukemia cell line was revealed that both they have similar ability to reduce cell viability. In association with their effects on peripheral blood mononuclear cell (PBMC) was demonstrated that *Origanum syriacum* Linn. has a more potent effect against PBMC but *Thymus vulgaris* L. leads to selective moderation. Based on findings of this study, given that *Thymus vulgaris* Linn. has selective therapeutic activity, therefore, its anticancer properties more than *Origanum syriacum* Linn. [45]

CONCLUSION: Here, we reviewed the role of plants in the treatment of leukemia based on their evaluations on different cell lines, animal models and cancer cells obtained from patients. In these studies, extracts prepared from plants had anticancer activity and leads to a reduction of cell viability **Fig. 1**. Induction of apoptosis was main mechanism to reduce cell viability through the increase of caspases activities, increase of intracellular Ca^{2+}, disturbance of mitochondrial membrane potential (MMP), reduction of mitochondrial outer membrane permeability, cytochrome c releasing and increase of BCl-2 protein level. In most studies, induction of apoptosis was confirmed by cell morphology changing and DNA fragmentation.

Meanwhile, It should be noted this point that the main factor to induce apoptosis was imbalance oxidant-antioxidant by an increase of reactive oxygen species (ROS) levels and free radical formation. Cancer cells have potential effect for growth; therefore; strategies related to cell growth inhibition can be helpful to treat leukemia. Here, we found treatment with extracts inhibit cell proliferation by mechanism involved to cell cycles such as arresting of G1/G0 and G2/M phases. Also, some extract involved in MAPK pathway and moderation of p53 protein level.

Interestingly, according to finding obtained from microarray analysis, during anticancer activity related to olive occurred high expression of genes related to K562 cells differentiation to monocyte/ macrophage lineage (IFI16, EGR1, NFYA, FOXP1, CXCL2, CXCL3, and CXCL8) that can be considered as an alternative strategy rather than other extracts. However, here it was confirmed that herbs have anticancer property but a treatment when is promising that performs as selective. Although these extracts had potential effects to reduce cancer cells but it was not examined selective treatment ability except for few cases. Finally, we suggest that should evaluate further studies to understand their ability as a selective treatment.

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