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Natural Compounds: Molecular Weapons against Leukemia's

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Abstract

Nowadays cancer is one of the main reasons of death all over the world and it is estimated that deaths caused by cancer will grow dramatically in the next decades. Even if chemotherapy is the election therapy for solid tumors, as well as leukemias and lymphomas, cancer treatments are in continuous evolution trying to solve the problem of resistance mainly due to low accumulation of the drug in tumor cells (MDR). Natural compounds represent a valid alternative to treat several disease and recently the scientific community focus on these natural compounds and plant metabolites with therapeutic activities and low toxicities compared with synthetic ones.

A combination therapy, that join conventional chemotherapy with natural plant metabolites, is now considered a new promising strategy to overcome MDR and reduce cellular toxicity; in particular, in leukemia due to its very complex origin and development of leukemogenesis.

Here, we want to summarize and update the recent applications of natural compounds in the treatment of leukemia.

Introduction

Nowadays, cancer is one of the main reason of death all over the world owing to late diagnosis, poor prognosis and, frequently, drug resistance. About 6 million people die of cancer each year, and it is among the leading causes of death worldwide; it is estimated that deaths caused by cancer will grow dramatically in the next decades.

Leukemia is an hematological disease caused by persistence of immature white blood cells in different district of the organism mainly bone marrow, lymph node, spleen and circulating blood. These immature white blood cells can proliferate generating the acute form of leukemia; otherwise, leukemia is due to the action of mature cells and in this case will be chronic leukemia. According to the cell lineage transformation and clinical characteristics, leukemia is classified in acute myeloid leukemia (AML), chronic myeloid leukemia (CML), acute lymphocytic leukemia (ALL) and chronic lymphocytic leukemia (CLL).

Chemotherapy is the election therapy for solid tumors, as well as leukemia and lymphomas [1]. Cancer treatments are in continuous evolution trying to solve the problem of low accumulation of the drug in tumor cells. Multidrug resistance (MDR) of tumor cells is often associated with an overexpression of ATP-binding cassette (ABC) transporter proteins that caused an ATP-dependent decrease in cellular drug accumulation [2]. Anticancer drugs, which elude the ABC transporters, could be a solution for drug resistance. Natural Compounds that reverse the resistance against anticancer drugs are considered multi-drug resistance (MDR) inhibitors or MDR modulators [3]. Recently, there is increased interest to identify multidrug resistance reversal compounds from plants having low or no side effects for use in cancer treatments [2].

It is evident that the ability to deliver the drug to target cells could be decisive to eradicate cancer. For this reason, nanotechnology-based drug delivery system seems to be very promising. Recently, some nanoparticles have been produced to hit specifically the bulk of the tumor, thanks to the use of specific markers for tumor targeted [4]. Moreover, in the last few years, the scientific community have described in edible plants the presence of exosomes that contain and/or carry pharmacological active molecules; for this reason, in 2014 the Food and Agriculture Organisation of the United Nations (FAO) created a database that describe the presence of exosomes in food, called FoodEVs. Exosomes are natural nanovesicles derived from intracellular late endosomes [5] that have been used as vehicle for therapeutic drug and gene delivery due to its versatility [6]. Accumulating evidence demonstrated that cancer cells release higher levels of exosomes suggesting their involvement in cancer progression and microenvironment education [7,8]. Leukemia derived exosomes can also affect bone marrow microenvironment thus enhancing leukemia cell growth [9-11]. We will discuss the anticancer effects of plants extracellular vesicles in a following section.

Many medicinal plants has been used yet in the past decades to treat several diseases due to their cardioprotective, hepatoprotective and antidiabetic activities [12]. Recently, the scientific community focus on natural compounds and plant metabolites with therapeutic activities, mainly phytochemicals such as polyphenolic, terpenes and lignans compounds, as new potential chemopreventive agents with cytotoxic activity, multidrug resistance reverting potential or apoptotic effects on cancer [13]. Furthermore, a combination therapy, that join conventional chemotherapy with natural plant metabolites, is now considered a new promising strategy to overcome MDR and reduce cellular toxicity; in particular, in leukemia due to its very complex origin and development of leukemogenesis.

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Here, we want to summarize and update the recent applications of natural compounds in the treatment of leukemia.

Anti- Leukemic Activities of Natural Compounds Produced By Plants

Polyphenols

Polyphenols are an important group of phytochemicals present in the plant kingdom that exert multiple protective functions against cellular oxidation, inflammation, aging, tumor initiation and progression. Recently, it was demonstrated that a diet with a regular consumption of fruits and vegetables, rich in polyphenols, significantly reduces the risk of many cancers. Some of the polyphenols studied for their anticancer potential are flavones, flavonols, isoflavones, and catechins. Tannins, present in many plant foods, are polyphenols that possess anticarcinogenic and antimutagenic potentials. It was demonstrated that the tannin resveratrol (3, 5, 4´-trihydroxystilbene), found in grapes and red wine, exhibits chemopreventive effects. Resveratrol is known to down regulate the high endogenous level of Heat shock protein 70 (Hsp70) in Chronic Myelogenous Leukemia K562 cells and induce apoptosis. It was demonstrated that resveratrol acts downstream of Bcr-Abl and inhibits Akt activity. This brings down the transcriptional activity of HSF1 and Hsp70 production in K562 cells [14].

In this section, among the polyphenols, we will discuss the role of Curcuminoids and Flavonoids.

Curcuminoids

These compounds are pigments present in dried rhizomes of *Curcuma longa* and are responsible for the yellow color of the plants. There are three compounds known as curcuminoids: curcumin, demethoxycurcumin, and bis-demethoxycurcumin [15]. We focus our attention on the role of *curcumin*, considered the king of spices. curcumin is a natural dietary polyphenol with documented anti-inflammatory, antioxidant and antineoplastic properties [16]; it is the most commonly used spice in India and in Ayurveda and traditional chinese medicine [17]. Several papers demonstrated that curcumin affects different steps of cancer progression. curcumin has been shown to be a strong suppressor of NF-kB that in turn down regulates the expression levels of NF-κB-regulated gene products; it inhibits the activation of IkB kinase (IKK) and, thus, prevents the phosphorylation of IkB and the subsequent translocation of NF-kB to the nucleus [17]. Curcumin also enhances cell death or apoptosis via inhibition of the MAPKs pathway, which includes c-Jun N-terminal kinases (JNKs) and extracellular signal-regulated kinases (ERKs) [16]. Moreover, Shah and colleagues indicate that Curcumin, as natural source, is able to overcome drug resistance as well as to reduce cytotoxicity profile of the conventional drug in Acute Myeloid Leukemia patients. They show that curcumin down regulates MDR genes, such as MDR1, LRP, BCRP and it has a synergistic effect in combination with cytarabine on primary leukemic cells. These data suggest that curcumin can be used as MDR modulator or chemosensitizer in combination with standard chemotherapeutic drug cytarabine [18].

It was found that curcumin induces expression of interferon regulatory genes (IFIT2) in leukemia cell lines. In leukemia, cells treated with IFNγ increased apoptosis and enhanced anticancer effect of curcumin. Conversely, shRNA-IFIT2 knockdown inhibited curcumin-induced apoptosis in U937 leukemia cells. These results demonstrated that there is a cross-talk between curcumin and interferon signaling pathways, which provides the basis for a new potential therapeutic approach, with curcumin combined to interferon [19].

Recent papers demonstrated that curcumin can induce epigenetic alteration such as changes in DNA methylation, histone modifications and modulation of several oncogenic and tumor suppressor microRNAs (miRNAs) expression such as miR-21, miR-20a, miR-17-5p, and miR-27a and miR-34 a/c [20].

Our research group showed, in in vitro and in vivo models, that treatment of CML cells with curcumin caused a miR-21-mediated modulation of PTEN/AKT pathway leading to the inhibition of leukemic cell growth. Curcumin affected the malignant properties of CML cells through a disposal of miR-21 in exosomes released by CML cells. Curcumin also induced the up-regulation of miR-196b and a decrease of BCR-ABL at mRNA and protein level. For these reasons, curcumin can be considered a promising compound that in association with conventional tyrosine kinase inhibitor, may improve the therapeutic approach for CML patients resistant to Imatinib [21]. Moreover, exosomes containing miR-21 and released by CML cells treated with curcumin were able to modulate the endothelial barrier organization and attenuated the angiogenic phenotype. These data suggest that curcumin could be a potential therapeutic agent for CML treatment with a double effect, on cancer cells and on tumor microenvironment [22].

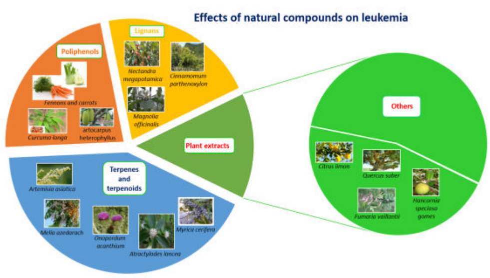

Figure 1: Effects of natural compounds on leukemia.

Numerous papers documented the protective effects of curcumin in leukemia malignancy. Pimentel-Gutiérrez and colleagues demonstrated, in Acute lymphoblastic leukemia (ALL), the potential effect of curcumin as pharmacological co-adjuvant of several chemotherapeutic agents used in ALL therapy [23].

There is a growing demand to find new therapeutic compounds that show not only lower toxicity but also more solubility and bioavailability. To answer to this request, recently different research groups work to develop derivates of natural compounds with these characteristics (Figure 1). It was identified a novel curcumin derivative with more potent antitumor activity than curcumin. This compound was shown to promote cell cycle arrest, at the G2/M phase, inducing apoptosis in the MDR chronic myeloid leukemia cell line [24].

A recent paper described the development of a stable polymeric micellar formulation of curcumin with improved solubility and stability and suitable, for this reason, for clinical applications in leukemia patients. Intracellular uptake to leukemic cells of curcumin-loaded polymeric micelles (CM-micelles) was higher than that of CM-DMSO; moreover, CM-micelles have a significantly higher cytotoxic activity than curcumin dissolved in DMSO on leukemic cells [25].

Flavonoids

Flavonoids are a class of polyphenolic compounds recently revalued for their anticancer properties. They can be used as adjuvant agents for cancer, in combination with conventional chemotherapy.

Luteolin: is a flavone isolated from the leaves of dandelion and sage plants but it is also contained in carrots, fennen and celery. Luteolin is widely studied because of its anti-cancer properties already demonstrated on different models of solid tumors [26,27]. The cytotoxic effect of luteolin was demonstrated recently also on two human CLL cell lines, HG-3 and EHEB. Sak and others demonstrated that Luteolin's effect on human CLL cell lines is due to the activation of the intrinsic apoptotic pathway mediated by caspases 3 and 9. Moreover other two flavonols, fisetin and quercetin, probably due to a specific binding to the cellular targets of signaling pathway induced by luteolin, are able to increase the cytotoxic activity of luteolin in both cell lines thus allowing that luteolin begin more effective at lower doses [28].

Artocarpesin and cycloartocarpesin are two flavones isolated from Artocarpus heterophyllus or jackfruit, a tree belonging from the family of Moraceae and native of South and Southeast Asia.

Among flavonoids, chalcones and their derivatives are known for their therapeutic effects as anti-inflammatory and anti-infective [29] or anticancer agent [30]. It has been previously demonstrated the cytotoxic effects of isobavachalcone on different carcinoma cell lines [31]. Recently Kuete et al. evaluated the cytotoxic effects not only of the chalcone isobavachalcone but also of others two flavonoids, artocarpesin and cycloartocarpesin, on drug-sensitive cancer cell lines and, for the first time, against MDR cancer cell lines. In particular, they demonstrated that these compounds induce, on MDR leukemia cells CCRF-CEM, apoptosis through activation of caspases, disruption of mitochondrial membrane potential and generation of reactive oxygen species (ROS) [32].

These results are promising and encouraging to further investigating on the role of these constituents in order to find novel cytotoxic drugs against multifactorial drug resistant cancers or compounds that are effective with reduced toxicity.

Terpenes and terpenoids isolated from plants

Terpenes are a big class of organic molecules produced mainly by conifers essential oils of the plant and generally used as natural agricultural pesticides. The terpenes could be modified chemically generating terpenoids that constitute about 60% of natural products. Plant terpenes and mainly terpenoids are used as fragrances and as traditional herbal remedies in alternative medicine. Because of their antioxidative or anti-inflammatory properties, these compounds are revalued as possible anticancer agents.

Triterpenoids induce cytotoxicity not only on sensitive leukemia cell lines but also in MDR cells. Recent findings have shown that these compounds interact with transporter proteins to inhibit drug efflux mediated by MDR1, MRP1 or BCRP. In particular, triterpenoids can act with different mechanisms, including direct interaction with the P-glycoprotein (P-gp) active site, stimulating the activity of the P-gp ATPase [33], or decreasing P-gp expression in a dose-dependent manner [34].

Myrica cerifera

Myrica cerifera is a tree that grows in the northern and central parts of America, Bermuda, and the Caribbean, commonly known as bayberry or wax myrtle. Several compounds have been extracted from the plant and some of them are known for their antioxidative and anti-inflammatory properties [35] or for their in vitro anticancer potential in some human cancer cell lines such as adenocarcinoma and prostate cancer cells [36], glioblastoma and melanoma cells [37].

Recently, Zhang and collaborators demonstrated that seven different triterpenoids isolated from the extract of *M. cerifera* bark hold cytotoxic activities against human breast cancer cell line SK-BR-3 and lung cancer cell line A549. Relatively to leukemia, they demonstrated the cytotoxic effect of one specific triterpenoid on human leukemia cell line HL60; furthermore their results showed that this compound activates not only mitochondrial mediated apoptotic pathway, via cleavage of caspase 3 and caspase 9, but also death-receptor mediated apoptotic pathway, via cleavage of caspase 8 [38].

Melia azedarach

Melia azedarach is a plant that grows preferentially in India, Cina and Australia. All components are tossic for humans if ingested, due to some neurotoxins mainly contained in the fruit. For this reason, ancients used the diluited infusion of leaves and bark to induce uterus relaxation or as sedative. Many studies focused on different compounds extracted from the plant, such as limonoids or triterpenoids, that exert cytotoxic activities [39,40]. Recently, new triterpenoids isolated from the fruit of *Melia azedarach* has been tested on human cancer cell lines including human leukemia cell line HL60, demonstrating their cytotoxicities thus opening new possibilities to use *M. azedarach* also for anticancer therapy [41].

Asteraceae species (*Artemisia Asiatica* and *Onopordum acanthium*)

Asteracee, known also as Compositae, are a family of plants largely diffuse. All the member of this family are enriched in secondary metabolites, including sesquiterpene lactones and pentacyclic triterpene alcohols and many of them are used to cure malignant disorders [42]. In particular, the shrub wormwood or Artemisia asiatica and the herbaceous plant of *Onopordum acanthium* are two plants used in traditional medicine for many diseases including cancers but their antiproliferative and cytostatic effects have been tested only against human adherent cancer cell lines [43,44].

In literature, there are not data about specific compounds isolated from these plants and their effects on Leukemia until 2015. Many sesquiterpenes isolated from these two plants has been recently investigated on human promyelocytic leukemia cells HL-60 in order to identify their antiproliferative effects. In particular, it has been demonstrated that four different sesquiterpenes exert these antiproliferative effects on HL60 affecting cell cycle and inducing apoptosis. The effects on cell cycle consist in an increase in the subG1 and G2/M populations, that indicate cell cycle arrest, while the activation of apoptosis has been demonstrated by the activation of caspase 9, as well as the nuclear fragmentation and the activation of effector caspase 3 [45].

Atractylodes lancea

Atractylodes lancea is a chinese herbal medicine. It is demonstrated that essential oils extracted from its rhizome exert apoptotic activity on human leukemia HL-60 cells. The main specific compounds responsible of these effects are b-eudesmol and the sesquiterpenoid hinesol [46]. Both compounds have cytotoxic activity on leukemic HL60 cells mediated by activation of apoptosis; this pathway is regulated by the activation of Jnk signaling, in the case of b-eudesmol [47]; instead, the sesquiterpenoid hinesol exert its effect on apoptosis through the regulation and balance between activation of the JNK and ERK pathways [48].

Quercus suber L.

Quercus suber L. is a tree widely diffuse in southwest Europe and northwest Africa, commonly known as cork oak. Recently, because of its antioxidant effects, it has been revaluated for nutraceutical applications. In particular, it seems that phenolic, aliphatic and triterpenic components obtained from the cork are responsible of these effects. A rising number of reports describe the pro-apoptotic effects of natural compounds in cancer cells and their effects on radical scavenging. Recently, Bejarano et al. described the antitumor effects of Quercus suber L. cork extracts (QSE) in human promyelocytic leukaemia cells HL-60, demonstrating that QSE is able to alter the mitochondrial outer membrane potential, activate caspase 3 and therefore induce apoptotic cancer cell death [48].

Lignans isolated from plants

Lignans are a large group of natural compounds extracted from different plants commonly known for its antioxidant properties and in balancing hormone levels.

Cinnamomum parthenoxylon: Cinnamomum is an evergreen tree native to South and East Asia. Cinnamomum belongs to genera of Lauraceae family that includes many species with different properties and commonly used as spices in food or as fragrances. Furthermore some of these species are used in traditional medicine and, relatively to species parthenoxylon, it has been demonstrated that the extract of the bark has antioxidant effects [49]. Several constituents of cinnamomum species have cytotoxic and apoptotic activities on various cancer cell lines [50]. Recently the scientific community investigate on possible anticancer effects of different constituents derived from the species c. parthenoxylon demonstrating the apoptotic effect of several lignans and phenylpropanoids isolated from its wood on human hepatoma cell line HUH-7 [51]. Adfa and colleagues demonstrate, in leukemia, that some fractions of C. parthenoxylon are able to induce morphological changes and to inhibit cell proliferation of leukemic cells HL-60 [52].

Nectandra megapotamica: Nectandra megapotamica is a plant native to Brazil, belongs to genera of Lauraceae family. It has been used in folk medicine to treat several diseases such as rheumatism and to relieve pain. Moreover, it has been demonstrated that different constituents isolated from the plant has pharmacological and biological activities [53]. There are not any studies regarding the cytotoxic activity against cancer cells of its extract and/or constituents of nectandra megapotamica. Recently Ponci et al. described the cytotoxic effects of different neolignans, extracted from the leaves of the plant, on human leukemic cells HL-60, demonstrating that these compounds exert their effects through activation of mitochondrial apoptotic pathway [53].

Magnolia officinalis: Magnolia is a flowering tree native to many regions in the world. Many species of Magnolia are traditionally used in Asian medicine, mainly its neolignan honokiol, extracted from the bark and the leaves of the tree. Honokiol is able to induce apoptosis and cell cycle arrest in non-small cell lung cancer [54] and in adult T-cell leukemia [55]. Recently it has been demonstrated that other natural compounds extracted from plants, such as green tea polyphenols and curcumin, exert their anti-cancer properties through the inhibition of the HDAC activity [56,57]. Li et al. demonstrated that honokiol inhibit cell growth of human leukemic cell lines and primary AML blasts through the same pathway mediated by HDAC proteins, thus suggesting honokiol as a novel nontoxic natural agent for cancer prevention and therapy in leukemia [57].

Collectively these results lead to try also the application of lignans extracted from different tree in the field of phytochemicals as anticancer agents.

Essential oils of algae extracts

Microalgae are unicellular species found in marine systems and generally used as biomass to produce energy. The biodiversity of microalgae is enormous and they are very rich in bioactive compounds, minerals, polysaccharides. Nowadays they are considered an important source to discover new bioactive compounds.

The current chemotherapy for AML is based on cytarabine, compound isolated from a marine sponge. There are few articles about the apoptotic effects of algae extracts on cancer cells. Goh et al. reported the apoptotic effects of Chaetoceros calcitrans microalga on MDA-MB-231 breast cancer cells [58], Prestegard's group instead showed the apoptotic effect of P. tricornutum microalgae extract on IPC81 rat myeloid leukemia cells [59]. Bechelli et al. showed that Dunaliella salina and Aphanizomenon flos-aquae inhibit the growth of both HL-60 and MV4-11 leukemic cell lines [60].

Recently it has been published a study on antileukemic activity of fifteen microalgae species to verify their potential for drug development. First of all the authors characterized the composition of essential oils of these fifteen different algae extracts and tested the different cytotoxic effects on HL60 and K562 leukemic cell lines. Afterwards, they selected five essential oils and investigated the pathways that determined the cytotoxic effects observed. This extracts are able to inhibit the activity of Akt on HL60 cells, while others increased the phosphorylation of MAPK on K562 cells finally activating apoptotic pathway mainly mediated by cleaved caspase 3 and cleaved PARP and the bcl-2 family protein BAD. The isolation of these essential oils from algae extract and their various combinations can allow to find new antileukemic agents more efficient and to reduce the toxicity because of their natural origin [61].

Extracellular vesicles in plants

Recently the interest of the scientific community toward extracellular vesicles (EVs) is grown; in the contest of natural compounds as new therapeutic molecules, the presence of exosomes in edible plants is up to now very interesting.

Already exist publications that describe the release of exosomes from tubers like carrot or ginger [62], from nuts and seeds sunflower [63] or from fruits like grape, watermelon or lemon. It is known that grapefruit nanovesicles, isolated from grape juice, act as immune modulators in the intestine and are able to attenuate inflammatory response in human disease [64]; furthermore there are clinical trials focus on their possible application to prevent cancer progression. It was demonstrated the uptake of watermelon-derived EVs in Caco-2 cells and mouse small intestinal stem cells suggesting that EVs could be the vehicle to transfer molecules in the intestine also due to their capability to remain intact in the gastrointestinal tract [65]. Raimondo et al. also demonstrated that the juice of citrus limon contains exosome-like nanovesicles. The fruit of citrus L. is commonly used in traditional medicine and its benefits are largely known, due to its content of citric acid and vitamin C, but also for its anti-cancer properties. In particular, they showed that these plant-derived nanovesicles are able to affect cell growth of human colorectal adenocarcinoma cells and leukemia cells. Furthermore, they confirmed the results in vivo on CML xenografts demonstrating that citrus nanovesicles reduce the growth of CML xenografts through activation of TRAIL-mediated apoptosis but also through inhibition of angiogenesis [66]. The authors show an alternative approach to cancer therapy based on plant-derived nanovesicles with antineoplastic capacity.

Differentiation inducers in AML and CML

Many natural compounds have been studied in these last years because of they are able to affect not only cell differentiation of solid tumors as chondrogenesis [67] and neuronal cells [68], but also of bone marrow-derived hematopoietic cells. Although the main differentiation inducer in acute promyelocytic leukemia therapy has been all-trans retinoic acid (ATRA), these compounds can support traditional anticancer chemotherapies or enhance the effect of ATRA [69].

Flueggea suffruticosa: Securinine is an alkaloid isolated from the flowering plant *Flueggea suffruticosa*, belonging to the family of Phyllanthaceae and commonly used as herb in traditional chinese medicine. Relatively to leukemia, Gupta et al. demonstrated that securinine induces growth arrest in AML cell lines, patient samples and AML tumors in nude mice thus confirming its possible therapeutic role for AML treatment. Nowadays it is considered a potential myeloid leukemia differentiation inducing agent; moreover it was shown that securinine enhances the differentiating activities of ATRA on leukemic HL60 cells, suggesting that this natural alkaloid could also be used in a combination therapy [70].

Veratrum californicum: Cyclopamine is another alkaloid isolated from the plant *Veratrum californicum* known as California corn lily, native to southwestern North America. Cyclopamine is studied as anticancer drug [71] and is also known to enhance HL60 cells differentiation, similarly to securinine, in association with ATRA [72].

Scutellaria baicalensis Georgi: On the contrary, the flavonoids wogonine and wogonoside induce AML cell differentiation independently of ATRA [73]. Wogonine is isolated from the chinese herb *Scutellaria baicalensis* Georgi, a flowering plant of the Lamiaceae family. It has been demonstrated that wogonine and its metabolite wogonoside have antioxidant and anti-inflammatory effects [74]; moreover wogonine induce cell cycle arrest, apoptosis and differentiation not only on different cancer cell lines [75], but also in hematologic malignancies where it induces apoptosis on malignant lymphocytes and suppresses cell growth of T-cells. Besides, wogonoside affects differentiation, acting on human AML cells in vitro and in vivo. In particular, wogonoside induces the monocytic differentiation of lymphoma cell line U937 and leukemic cell line HL60 [76].

In addition, wogonine exerts effects on CML cell line K562 and, interestingly, on imatinib resistant K562 cells.

Wogonine lead to differentiation of K562 cells, demonstrated by the increased expression of many markers and by the cell cycle arrest at the G0/G1 phase with inhibition of the MAPK pathway. Furthermore, it exerts its effect also on differentiation of primary CML cells from patients and on resistant K562 cells probably with a mechanism Bcr-abl independent [77].

Another mechanism through which is reactivated erythroid differentiation in K562 cells is the inhibition of heat shock protein HSP90. Many natural compounds are able to do this in combination or not with the inhibition of Bcr–Abl and finally activate the erythroid transcription factor GATA-1. Wogonin induces erythroid differentiation in K562 cells mediated by activation of GATA-1 and inhibition of Bcr–Abl [77].

Monocillium nordinii and dandelion plant

The compounds radicicol, isolated from the mushroom Monocillium nordinii, and apigetrin, extracted from the root of dandelion plant, act on erythroid differentiation too. Radicicol exert its effect on Bcr-Abl degradation and HSP90 inhibition through increasing of GATA-1 and inhibition of the transcription factor PU.1, an inhibitor of erythropoiesis [78]. Apigetrin induces the expression of GATA-1 but also it is able to inhibit the expression of different markers, such as CD11b (granulocyte), CD14 (monocyte) and CD41a (megakaryocyte) [79]. These examples demonstrate that many compounds extracted from different herbs or root exert their effect on leukemia cell differentiation thus inhibiting, in an alternative way, cell proliferation.

Efforts to combat cancers in terms of chemotherapeutic drugs have not been effective enough and those that show promising results exhibit side effects and poor bioavailability. Natural products, that are a part of our daily diet or are easily obtained and disposable, have shown considerable anti-neoplastic effects without causing side effects[80]. Here we showed some examples of natural compounds extracted from plants and their role recently discovered as anti-leukemic agents.

Conclusion

Overall, plant extracts, which have historically been used as therapeutic agents, are continuously revealing novel anticancer properties and mechanisms and continue to hold prominent promise in future cancer therapies. The experimental data showed here, encourage the scientific community to enhance the research on drugs of natural origin with lower toxicity and easily disposable that could be used as valid alternative to chemotherapy or in combination with, thus counteracting drug resistance, decreasing cytotoxic effects and improving the patient's quality of life in leukemia as well as in other cancer types.

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