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REVIEW ARTICLE

Established Human Cell Lines as Models to Study Anti-leukemic Effects of Flavonoids

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Abstract: Despite the extensive work on pathological mechanisms and some recent advances in the treatment of different hematological malignancies, leukemia continues to present a significant challenge being frequently considered as incurable disease. Therefore, the development of novel therapeutic agents with high efficacy and low toxicity is urgently needed to improve the overall survival rate of patients. In this comprehensive review article, the current knowledge about the anticancer activities of flavonoids as plant secondary polyphenolic metabolites in the most commonly used human established leukemia cell lines (HL-60, NB4, KG1a, U937, THP-1, K562, Jurkat, CCRF- CEM, MOLT-3, and MOLT-4) is compiled, revealing clear anti-proliferative, pro-apoptotic, cell cycle arresting, and differentiation inducing effects for certain compounds. Considering the low toxicity of these substances in normal blood cells, the presented data show a great potential of flavonoids to be developed into novel anti-leukemia agents applicable also in the malignant cells resistant to the current conventional chemotherapeutic drugs.

Keywords: Antiproliferation, Apoptosis, Cell cycle arrest, Cytotoxicity, Differentiation, Flavonoids, Leukemia, Human cell lines.

1. INTRODUCTION

Leukemia as a malignant tumor of the hematopoietic system is a commonly diagnosed neoplasm that causes significant harm to human health and represents a major cause of cancer-related deaths worldwide [1-7]. Leukemia accounts for almost 5% of all cancer cases ranking in the sixth place among various human malignancies [4, 6]. Furthermore, it is the most common neoplasm in childhood being the cause of about 30% of all cancer-related deaths in children and adolescents under the age of 14 years [6, 8-10].

There are multiple risk factors of leukemogenesis including endogenous and exogenous exposures, genetic vulnerability and susceptibility, but also the chance might play its role. However, the precise cause of leukemia is still not known [7, 8, 11]. Like other cancers, also leukemia is characterized by a succession of mutations in genes that regulate the processes of cellular division, death and differentiation leading to the progressive shift of cells from normal to malignant state [8, 11-15]. Hematopoietic cancers often emerge in consequence of the uncontrolled growth and accumulation of immature blasts as the cellular differentiation is typically blocked at a particular maturation stage leading to the deficiency of normal functional blood cells and causing numerous serious symptoms [16-20]. Such failure in the cellular development makes leukemia the disease of cell differentiation [19]. Moreover, recent studies have shown that tumors of blood-forming tissues can be originated from leukemic stem cells rendering leukemia also a stem cell disorder [21, 22].

Leukemia consists of a heterogeneous group of hematological malignancies affecting the cells of all hematopoietic lineages [8, 10, 20, 21]. This complex disease can hit all the age groups being somewhat more common in men than in women and developing more frequently in Caucasians compared to other races [7, 10]. On the ground of involved cell types and the temporal progression of disease, four main types of leukemia are distinguished: acute lymphocytic leukemia (ALL), chronic lymphocytic leukemia (CLL), acute myelogenous leukemia (AML) and chronic myelogenous leukemia (CML), as described elsewhere [7, 23-26]. ALL is the most common form of childhood malignancies with the highest prevalence between the ages of two and five years, constituting about one-third of all pediatric cancers, as indicated in [7, 10, 24, 27, 28]. Although more than 80% of children with ALL are currently cured, the survival rate of adults suffering from ALL rarely exceeds 40%, as reviewed in [28, 29]. The other lymphoproliferative malignancy, CLL is the most frequent type of leukemia in adult population in the Western countries affecting mainly the people over the age of 55 [24, 30-33]. Despite the numerous studies, this highly heterogenous disease is still considered incurable [32-36]. Similarly, the overall survival of patients with AML has re-

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mained poor whereas the incidence of this aggressive malignancy is continuously increasing [37-47].

The current treatments of leukemia include chemotherapy, radiation, and bone marrow transplantation, whereas chemotherapy has still remained the most important intervening strategy in treating different types of hematological malignancies [4, 8, 10, 26, 48-53]. However, standard chemotherapy agents are usually expensive and often associated with toxicity towards normal cells resulting in serious side effects and limiting the overall efficacy of drugs [3, 8, 10, 26, 49, 52, 54-56]. In addition, drug resistance also represents a major problem in the current treatment of leukemia [5, 8, 13, 52, 57-60]. Such chemoresistance can be either intrinsic or acquired after initial therapy being a main reason for treatment failure [13, 61-64].

Recently, introduction of targeted therapies have brought about considerable improvements in survival of patients with certain types of leukemia; at that, all-trans retinoic acid (ATRA) for AML and Imatinib against CML represent two examples of the success of target-based therapies [8, 27, 65-67]. Using the agents that force immature leukemia cells to undergo terminal differentiation or so-called differentiation therapy, is potentially a less toxic alternative to treat hematopoietic neoplasms [13, 17-19, 40, 53, 54, 68-70]. Indeed, granulocytic differentiation induced by ATRA is proven to be clinically effective for treatment of acute promyelocytic leukemia (APL) leading to a breakthrough in cure of this AML subtype [12, 16, 20, 38, 71-75]. However, application of differentiation therapy can be effective only in certain forms of leukemia and the treatment might be accompanied by severe side effects as well as development of resistance [20, 73-77].

Management strategies of CML have made a significant progress after the discovery of Imatinib as a selective protein tyrosine kinase inhibitor against a fusion protein, namely breakpoint cluster region-Abelson murine leukemia (BCR-ABL) [10, 22, 23, 65, 70, 78-81]. This chimeric protein is formed as a consequence of a reciprocal translocation between chromosomes 9 and 22, and its constitutive tyrosine kinase activity contributes to antiapoptotic mechanisms, uncontrolled cell proliferation and survival advantage in CML [22, 23, 65, 70, 78, 80-84]. However, despite the initial therapeutic efficiency of Imatinib, development of resistance and disease relapse are still serious problems for most patients [23, 65, 70, 78, 80-83]. In addition, the use of new generation inhibitors specifically targeting the tyrosine kinase domain of Bcr-Abl, such as Dasatinib and Nilotinib, can also be limited due to emergence of resistance and adverse effects of these agents [23, 78, 80, 81].

Thus, regardless of the progress in studies of leukemogenesis and improvements of clinical management schemes, the cure rate of hematological malignancies has still remained unsatisfactory and mortality is high [1, 9, 10, 13, 20, 49, 51, 85]. Therefore, novel effective therapeutic strategies to improve the prognosis and quality of life of patients with leukemia and reduce the treatment-related morbidity and mortality rate are highly needed [10, 28, 42, 45, 52, 86]. Hence, discovering the newer agents with lower nonspecific toxicity and higher efficacy, especially towards the otherwise drug-resistant cancer cells, has become an important focus for current leukemia research [8, 25, 49, 51-53, 62, 87].

2. NATURAL RESOURCES FOR NOVEL ANTICANCER AGENTS

Over the past decades, there is an increasing interest in the use of bioactive components from natural sources as potential novel anticancer agents, and identification of chemical entities, molecular targets and signaling pathways triggered by these natural products has become a very important topic of research [2, 10, 11, 30, 88-92]. Nature provides a tremendous diversity of candidate compounds for fighting cancer, including hematological malignancies, whereas modification of these lead molecules can further enhance their efficacy and reduce adverse effects [6, 9, 13, 15, 28, 39, 49, 93-95]. Accordingly, many clinically used anticancer drugs are either natural products or obtained by derivatization of naturally occurring lead compounds [62, 96-98]. Indeed, as a matter of fact, up to 70% of chemotherapeutic drugs approved by the US Federal Drug Administration are derived from natural sources [15, 12, 24, 27, 28, 89, 99-102]. Examples of such agents include Vinca alkaloids vincristine and vinblastine, taxanes (Paclitaxel and Docetaxel), podophyllotoxin derivatives (etoposide and teniposide), and camptothecins like topotecan [11, 24, 28, 37, 95, 103-106]. Especially the plant-derived compounds have made a major contribution to the arsenal of current anticancer drugs; however, still less than one-tenth of all terrestrial plants is evaluated for their possible cytotoxic activity [95, 107, 108]. An important advantage of natural product-based antineoplastic substances for clinical application is their low nonspecific toxicity [13, 49, 109, 110]. Moreover, these compounds are usually effective in different phases of carcinogenesis interacting simultaneously with multiple molecular targets and triggering several cellular pathways [15, 111].

3. FLAVONOIDS AS PHYTOCHEMICALS WITH POTENTIAL ANTICANCER PROPERTIES

Flavonoids are naturally occurring compounds with abundant occurrence in plants and plant-derived foods representing nutritionally valuable constituents of the daily human diet [38, 81, 82, 87, 100, 112-120]. These low molecular weight polyphenols are widely distributed in fruits, vegetables, grains, seeds, nuts, spices and medicinal herbs, but also in beverages like tea, coffee, wine and beer [6, 98, 121-129]. The human dietary consumption of flavonoids varies largely being about 20 mg to 1 g per day, depending on the population and regional and cultural dietary habits [97, 118, 121, 130-135]. More than 5000 different flavonoids have been described from nature indicating their huge structural diversity [8, 18, 104, 136-140]. These compounds consist of two aromatic rings (A and C), linked through an oxygenated heterocycle (ring C) [18, 32, 34, 98]. The basic structure of flavonoid skeleton C6-C3-C6 is depicted in (Fig. **1**). Depending on the molecular organization and modifications, flavonoids are categorized into various subclasses, mainly flavonols, flavones, flavanols or catechins, flavanones, isoflavones, and anthocyanidins [90, 96, 114, 133, 138, 141].

Flavonoids as plant secondary metabolites were primarily recognized as biological pigments providing the color to

flowers and fruits [8, 23, 58, 138, 142]. However, these compounds are involved in a wide range of processes in plant physiology including interspecies interaction, protection from ultraviolet radiation and photosynthetic stress, defense against microorganisms, fungi and pests [2, 61, 104, 120, 142-145]. In addition to their roles in plants, flavonoids exhibit a remarkable spectrum of pharmacologically important biological activities in humans. Indeed, they can exert antioxidant, antimicrobial, antiinflammatory, antidiabetic, antidiarrheal, antiallergic, antiatherosclerotic, anxiolytic, antispasmodic, antithrombotic, antimutagenic, antiviral, immunomodulatory, hepatoprotective, gastroprotective and cardioprotective effects [6, 24, 81, 90, 123, 124, 137, 139, 142, 146, 147]. Moreover, flavonoids have been shown to reveal also anticancer properties, both *in vitro* and *in vivo*, including antileukemic activities [8, 45, 87, 100, 113, 140, 148-151]. Importantly, these polyphenolic compounds may behave as dietary chemopreventive agents by blocking neoplastic inception or retarding tumor progression [2, 19, 77, 105, 115, 126, 143, 152]. There is indeed accumulating experimental and epidemiological evidence that increased intake of plant-based products, i.e. diets rich in flavonoids provide protection against malignancies and are associated with a reduced cancer risk [1, 19, 51, 118, 135, 153]. Furthermore, due to their multiple cellular mechanisms and low side effects, flavonoids possess a great potential in developing of novel chemotherapeutic drugs [125, 139, 153, 154].

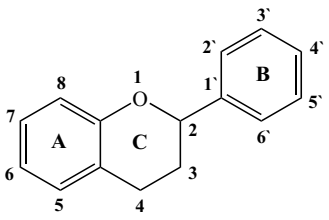

Fig. (1). Basic structure of flavonoids.

4. MODULATION OF CANCER HALLMARKS BY FLAVONOIDS

Multiple biochemical mechanisms have been linked to anticancer activities induced by flavonoids [8, 80, 135, 138, 153, 155]. At that, these plant secondary metabolites can interfere with different hallmarks of cancer, which represent the characteristic capabilities acquired during the multistep process of tumorigenesis [156], as depicted in (Fig. **2**). Uncontrolled cell proliferation is one of those hallmarks and flavonoids are shown to be able to exert growth inhibitory and antiproliferative effects in malignant cells by modulating various signal transduction pathways [8, 14, 90, 91, 96, 98, 118, 133, 135, 153, 157-160].

Another important hallmark of cancer cells is their evasion of apoptosis and compounds that promote the programmed cell death are considered as new attractive candidates in combating cancer [11, 13, 15, 27, 109, 126, 141, 161-163]. In this way, the ability of some flavonoids to induce cancer cell apoptosis might be a relevant mechanism for eliminating of neoplasms [11, 14, 18, 44, 90, 91, 135, 158, 164]. Apoptosis can be induced through intrinsic or extrinsic pathways, with caspases as the key executioners of programmed cell death [2, 165, 166]. The extrinsic pathway is activated by death receptors locating in cell surface, while the intrinsic pathway triggers proapoptotic events in mitochondria [58, 81, 126]. Although it is well known that flavonoids can exhibit both antioxidative as well as prooxidative properties, production of intracellular reactive oxygen species (ROS) is proposed to play an important role in the apoptotic signaling [6, 17, 86, 164, 167-171].

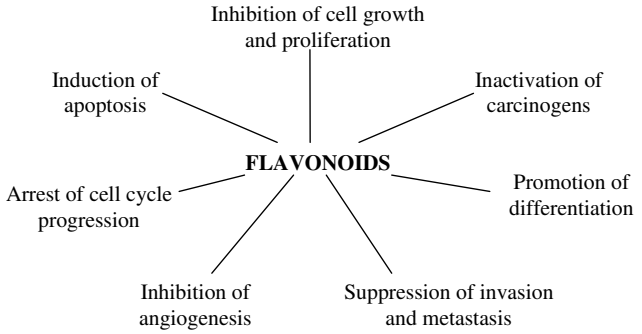

Fig. (2). Effects of flavonoids in cancer cells.

Malignant growth is characterized also by disturbances in cell cycle regulation and loss of checkpoints, making cell cycle machinery a potential target for novel antitumor drugs [172-175]. Flavonoids are shown to arrest cell cycle progression either at the G0/G1 or G2/M phase, depending on their structure and concentration [90, 91, 118, 165, 176-179]. As tumor cells are typically characterized by different mutations in cell cycle regulating genes, the same flavonoid can cause cell cycle arrest in different phases depending on the certain cellular model [118, 159, 176]. Plant flavonoids can also induce or enhance the differentiation of cancer cells [12, 18, 77, 94, 96, 109, 138, 180], inhibit angiogenesis [8, 96, 98, 109, 143], or block the processes related to invasion and metastasis, as depicted in (Fig. **2**), and reviewed elsewhere [8, 96].

Tumor angiogenesis is an essential hallmark of carcinogenesis as new blood vessels might supply progression and metastasis [143]. Uncontrolled angiogenesis promotes the growth of neoplasm through acting on various key proteins, such as vascular endothelial growth factor (VEGF) and its receptor as well as different matrix metalloproteinases (MMPs). Flavonoids are well known to regulate the expression of these molecules and the activity of respective signaling pathways, leading to antiangiogenic effects and limiting the promotion of tumor [94, 96, 98, 109]. Furthermore, one of the important mechanisms by which flavonoids may exhibit their cytoprotective antitumor properties is through a modulation of carcinogens' metabolism [90, 96, 98, 109, 135, 181]. Indeed, flavonoids can interact with different phase I and phase II enzymes responsible for the biotransformation of various xenobiotics, interfering thus with the metabolic activity of potential mutagens and carcinogens [96, 98, 109, 135].

It is generally accepted that the biological activities of flavonoids depend largely on their chemical structure and spatial orientation of various moieties on flavonoid backbone [8, 18, 124, 137, 138, 160, 182, 183]. Indeed, even minor changes in the flavonoid structure may strongly influence its

biochemical and biological properties making it possible to achieve pharmacologically more potent derivatives through the further structural modification [8, 118, 120, 184]. Although it has been suggested that free hydroxyl groups and the presence of a C2-C3 double bond are necessary features for anticancer activities [98, 118, 132, 135, 169, 185, 186], it is still generally agreed that the antiproliferative effects of flavonoids cannot be predicted just based on the chemical composition and structure [118, 135, 185]. Therefore, it is important to study each flavonoid systematically to realize its potential therapeutic efficacy in the fight against cancer [140].

5. BIOAVAILABILITY AND BIOCONVERSION OF FLAVONOIDS

Although multiple studies indicate the anticancer activities of flavonoids, application of these polyphenols in clinical treatment or chemoprevention is still limited due to their overall poor bioavailability and extensive bioconversion [10, 20, 96, 129, 131, 186-189]. Flavonoids exist in plants mainly as glycosides or as free aglycones [18, 96, 138, 140, 188, 190, 191]. After intake, these molecules undergo extensive metabolism and as the first step, flavonoid glycosides are hydrolyzed to aglycones in the small intestine [32, 40, 188, 191-193]. The metabolism is followed by conjugation reactions with methyl and sulfate groups and glucuronic acid in the small intestine, but also in the large intestine and colon [10, 32, 34, 113, 131, 153, 187, 188, 191, 194]. The metabolic conversion is completed in liver and flavonoids enter the bloodstream mainly in the form of different conjugates [32, 134]. It is generally accepted that any alteration in flavonoid structure can bring about important changes in biological activities and the anticancer properties of circulating metabolites can be different from that of the parent compounds [40, 113, 153, 188, 195, 196]. Therefore, it is possible that some effects previously published in the literature can even belong to the certain conjugates rather than the flavonoid aglycones themselves [131, 195].

Due to the rapid metabolism, the blood concentrations of flavonoids after intake of flavonoid-rich foods usually remain below 10 μM [10, 32, 92, 116, 121, 133, 134, 136, 145, 153, 192, 197-203]. However, the higher plasma levels (even up to 400 μM) can be transiently achieved by intravenous injection [59, 138, 189]. Moreover, it is possible that certain cells or tissues accumulate elevated concentrations of flavonoids; the higher content of these polyphenols is indeed found at the sites of inflammation [32, 121, 133, 192, 196, 198, 204].

It is also shown that methylated flavonoids are in general metabolically more stable than respective unmethylated aglycones [111, 168, 186, 187]. In addition, the stability and bioavailability of flavonoids have been improved via synthetic modifications, protecting reactive hydroxyls by acetate groups [52, 72, 78, 170]. Recently, it has been reported that acylation of phloridzin, a flavonoid glycoside with different fatty acids can significantly impact its chemotherapeutic potential in acute monocytic leukemia THP-1 cells [205].

Recently, the nanotechnological approaches to increase the bioavailability of flavonoids have been introduced by encapsulating these plant secondary metabolites in nanostructured liposomal carriers and targeted delivering to tumor cells [25, 60, 72, 189, 206, 207]. Such systems can improve the stability and solubility of flavonoids and elevate their local concentrations at the target area providing thus a promising strategy for pharmaceutical application of flavonoids in the future [161, 206, 208].

6. HUMAN CELL LINES USED IN ANTILEUKEMIC STUDIES OF FLAVONOIDS

Over the years, various human leukemia cell lines have been established and used *in vitro* anticancer studies of flavonoids, as summarized in (Table **1**) and reviewed elsewhere [77, 98, 209]. These models provide an important tool for evaluating cytotoxic and differentiation inducing potencies of polyphenolic agents with potential therapeutic activity [16, 113, 162, 210]. As sensitivities to bioactive compounds and their molecular mechanisms can vary among different cell lines, the use of more than one model is considered necessary for identifying novel leads of antileukemic agents [98, 164, 211]. For execution of a comprehensive study on the *in vitro* anticancer action of natural flavonoids in human leukemia cell lines, the data about different antileukemic activities, including growth inhibitory and apoptogenic effects as well as blocking cell cycle progression and inducing cellular differentiation, previously published in the literature were compiled and examined. To facilitate this large-scale work, only the activity data of natural flavonoids in human leukemia cell lines were explored. The main tendencies and conclusions of this extensive analysis are presented in the following sections.

6.1. Differential Cytotoxic Effects of Flavonoids on Human Leukemia Cells

Numerous studies have demonstrated that flavonoids can display antiproliferative and cytotoxic effects in human leukemia lines by measuring the decrease of cellular viability following the treatment of cells with structurally different polyphenols. The efficacy of these responses is quantitatively characterized by IC_{50} values representing drug doses required to reduce the cell growth by 50%. In the current work, these constants were compiled from the literature and presented concisely in (Table **2**) making it possible to bring forth some characteristic features of the action of flavonoids in models of hematological malignancies.

Multiple distinct and interactive molecular mechanisms and signaling cascades have been demonstrated to be involved in the anticancer effects of flavonoids influencing cellular proliferation, cell cycle progression, and apoptosis. Furthermore, simultaneous action on different cellular targets may help to fight against cancer and prevent emergence of drug resistance [34, 35, 111, 201, 202, 212, 213]. Although several flavonoids are able to induce programmed cell death in different leukemia types (Table **2**), making these plant secondary metabolites potentially attractive chemopreventive or chemotherapeutic agents, and both intrinsic as well as extrinsic apoptotic pathways are shown to participate in these ROS-dependent or -independent processes [25, 131, 166, 170, 175, 214-217]. The precise mechanisms regulating flavonoids-triggered cellular destruction are not fully understood [48, 72, 218-220]. However, a thorough analysis

Table 1. Characterization of human leukemia cell lines commonly used in anticancer studies of flavonoids.

Cell Line	Disease	Characteristics	References
HL-60	APL, derived from an adult female patient	AML-M2 myeloblasts, poorly differentiated cells; useful model for studies of differentiation with ATRA and DMSO causing neutrophilic differentiation, TPA and 1,25 (OH) 2D3 inducing monocytic maturation; p53-deficient	[12, 17, 21, 42, 44, 54, 77, 92, 93, 101, 120, 131, 148, 168, 183, 239, 242, 254, 256, 261, 262]
NB4	APL	AML-M3 promyelocytes; t(15;17) translocation fusing the RARα and PML genes; useful model for studies of differentiation along granulocytic or monocytic/ macrophagic lineage	[12, 38, 44, 73]
KG1a	AML	p53-deficient	[10]
U937	AML, derived from a patient with diffuse histiocytic lymphoma	AML-M4/M5 monoblasts; useful model for studies of differentiation with ATRA, TPA and 1,25 (OH) 2D3 inducing differentiation into monocytic/ macrophagic lineage; p53-deficient	[10, 12, 16, 42, 44, 148, 168, 209, 242, 263-265]
THP-1	AML	AML-M5 cells, mature monocytes, a well-differentiated line; p53-deficient	[10, 42, 131, 188]
K562	CML, derived from a patient with blast crisis	Pluripotent cells; useful model for studies of differentiation toward erythrocytic, granulocytic, monocytic or megakaryocytic lineages with Imatinib and cyclosporine A causing erythrocytic differentiation and TPA inducing megakaryocytic maturation; expression of Bcr-Abl fusion oncogene; p53-deficient	[10, 18, 19, 22, 49, 70, 76, 77, 82, 83, 112, 134, 138, 168, 209, 263, 266, 267]
Jurkat	T-ALL	P-gp-negative; p53-deficient	[10, 103, 246]
CCRF-CEM	T-ALL	p53-deficient	[10, 95, 244]
MOLT-3	T-ALL, cells released after chemotherapy	Wild type p53, mutant for PTEN	[10]
MOLT-4	T-ALL, established from a patient with relapsed disease after multidrug chemotherapy		[209, 252, 268]

1,25 (OH) 2D3, 1α, 25-dihydroxyvitamin D3; ALL, acute lymphocytic leukemia; AML, acute myelogenous leukemia; APL, acute promyelocytic leukemia; ATRA, all-trans retinoic acid; Bcr-Abl, breakpoint cluster region-abelson murine leukemia; CML, chronic myelogenous leukemia; DMSO, dimethyl sulfoxide; P-gp, P-glycoprotein; PML, promyelocytic leukemia-associated protein; RARα, retinoic acid receptor-α; TPA, 12-O-tetradecanoylphorbol-13-acetate.

of various signaling cascades involved in antileukemic effects of flavonoids is recently reported showing multiplicity of molecular targets of these polyphenols in blood cancer cells [221].

Flavonoids might express their cytotoxic effects on cancer cells, including leukemia cells through multiple pathways and various molecular mechanisms, such as induction of intrinsic and extrinsic apoptotic pathways, activation of various protein kinases (*e.g.* AMP-activated protein kinase, phosphatidylinositol-4, 5-biphosphate-3 kinase, mitogen activated kinase, protein kinase C, and death-associated protein kinase 2), specific estrogen and androgen receptors, various transcription factors (*e.g.* tumor protein p53, nuclear factor-kappaB), drug efflux pumps (*e.g.* P-glycoprotein), and heat-shock proteins. The anticancer activity of flavonoids in various cancer cells of blood origin can occur either dependent or independent on ROS production due to the structure and properties of certain flavonoids and the specific leukemia cell lines, as reviewed elsewhere [214-217, 221]. As the precise signaling pathway (s) and molecular mechanism (s) still remains largely elusive, the unraveling of these pathways is of ultimate importance to better understand and support the use of the flavonoids in antileukemia chemotherapeutic regiments.

In recent years, the question has been arisen as to whether the anticancer properties of flavonoids depend mostly on cell types or are rather specific to flavonoids implicating that a certain polyphenol acts similarly in different cells [8, 10]. Probably both of these options are valid and targeted signaling proteins depend on the flavonoid structure as well as cellular context. Indeed, on the one hand, various leukemia lines display somewhat differing sensitivities towards various polyphenolic agents, as indicated in (Table **2**), and described elsewhere [8, 10, 18, 90, 115, 134, 140, 164, 222]. In this way, chronic myeloid leukemia cell line K562 has been shown to be more resistant to apigenin and luteolin than promyelocytic leukemia HL-60 cells [8, 150]. Also, oroxylin A exhibits higher susceptibility to HL-60 and U937 than K562 cells [38]. However, acacetin is cytotoxically more potent in acute T-lymphoblastic leukemia Jurkat cells than in myeloid lines HL-60 and U937, whereas K562 cells are almost unaffected by this compound [126]. Quercetin shows growth inhibitory activity in both myeloid and lymphoid leukemia lines, however, this compound is more active

Table 2. Differential cytotoxicity of flavonoids in various human leukemia cell lines.

Flavonoids	Time, h	Mean IC_{50} Value ± Standard Error, μM (Number of Published Constants)*										References
		HL-60	NB4	KG1a	U937	THP-1	K562	Jurkat	CCRF-CEM	MOLT-3	MOLT-4	
FLAVONES												
Apigenin	24 48 72 96	60.0±20.8 (3) 23.2±7.9 (3) 28.0±5.6 (4) 29.2±1.7 (1) Apoptosis	34 (1)	500 (1) Apoptosis	112.4±47.7 (2) 40.3±10.3 (2) 28.2±13.2 (2) 39.7±2.1 (1) Apoptosis	108.9±71.1 (2) 31.9±3.2 (1) 31.9±2.7 (1) 27.8±3.9 (1) Apoptosis	275.0±75.0 (2) 75.4±26.6 (5) 39.8±18.9 (3) 42.5±6.0 (3) Apoptosis	91.5±51.6 (2) 35.8±2.6 (1) 28.5±0.5 (2) 29.6±1.6 (1) Apoptosis	195 (1) Apoptosis	140 (1) Apoptosis		[8, 10, 75, 84, 129, 132, 134, 144, 173, 179, 181, 207, 260-264]
Baicalein	24 48 72 96	25…30 (1) 23.4±0.4 (2) 14.2±0.2 (2) 0.96 (1) Apoptosis	10 (1)		22 (1)		21.3±1.2 (1) 14 (1) 24.3±2.5 (2) Apoptosis	9 (1)	48.6±0.8 (1) 33.4±1.9 (1) 39.2…75.9 (1) Apoptosis		23.4 (1) 8.6 (1)	[8, 25, 46, 132, 225, 227, 244, 262-266]
Chrysin	24 48 72 96	328 (1) 180 (1) Apoptosis	134 (1)	335 (1) Apoptosis	217 (1) 16 (1) 150 (1) Apoptosis	500 (1) Apoptosis	340 (1) 40±6 (1) 180 (1) 59.4±5.5 (2) Apoptosis	180 (1) 78.7 (1) Apoptosis	128 (1) 79.8 (1)	217 (1) Apoptosis		[8, 10, 74, 92, 132, 261, 262]
Flavone	72 96	257 (1) 19.8 (1)					80.1±1.3 (2) Apoptosis				>45.0 (1)	[121, 132, 262, 265]
3-Hydroxyflavone	48						191.9 (1) Apoptosis	81.3 (1) Apoptosis				[23, 92]
Luteolin	24 48 72 96	11.6±3.8 (3) 19.8±7.4 (4) 15.0±1.1 (1) Apoptosis	10 (1)		36 (1) 28 (1) 14.5±5.5 (2) Apoptosis		90 (1) 61.6±17.8 (3) 66.3 (1) 30.7±2.0 (2) Apoptosis	6 (1)				[8, 53, 84, 132, 134, 203, 222, 261-264, 267-269]
Scutellarein	48	33.7 (1)										[263]
Tricetin	48	31.3 (1) Apoptosis										[114]
O-methylated flavones												
Acacetin	24	59.1 (1)			45.7 (1)		≥100 (1)	25.8 (1) Apoptosis			59.1 (1)	[120]
Chrysoeriol	48	28.9 (1) Apoptosis										[114]
Diosmetin	48	28.5 (1) Apoptosis										[114]
Eupatorin	72	~5 (1) Apoptosis			~5 (1) Apoptosis					~5 (1) Apoptosis		[209]
Nobiletin	24 72 96	41.5±7.0 (1) 52 (1) 0.25 (1) Apoptosis									12.6 (1) >24.9 (1)	[121, 244, 265, 270, 271]

(Table 2) contd….

Flavonoids	Time, h	Mean IC_{50} Value ± Standard Error, µM (Number of Published Constants)*										References
		HL-60	NB4	KG1a	U937	THP-1	K562	Jurkat	CCRF-CEM	MOLT-3	MOLT-4	
Oroxylin A	96	37.8 (1) Apoptosis	92.6 (1) Apoptosis		65.5 (1) Apoptosis		88.4 (1) Apoptosis					[35, 68]
Tangeretin	24 72 96	>100 (1) 32 (1) 0.062 (1) Apoptosis					42.4±13.6 (1) 31.2±6.4 (1) Apoptosis				14.0 (1) 13.0 (1)	[76, 121, 244, 246, 271]
Wogonin	24 48 72 96 120	~50 (1) 17.4 (1) 0.56 (1) Apoptosis	 39.3±3.1 (1) Apoptosis		37.2…72.1 (1)	 Apoptosis	37.3…72.1 (1)	 Apoptosis	37.3…72.1 (1) Apoptosis		30.7 (1) 9.4 (1) Apoptosis	[67, 187, 206, 220, 227, 244, 263, 265]
Flavone glycosides												
Apigetrin	48	>95.5 (1)										[188]
Baicalin	24 72	48.8 (1) 36.8±1.1 (1) Apoptosis			23.7…45.9 (1)		23.7…45.9 (1)	 Apoptosis	23.8 (1) Apoptosis			[34, 225, 227, 272]
Homoorientin	48	>100 (1)										[222]
Scutellarin	24 48 72	118.1 (1) 21.7±6.4 (1) 35 (1)	 165 (1)		 58 (1)	77.9 (1)	 26.2±1.8 (1) 73 (1)	23.0 (1) 63.0 (1)	38.3 (1)			[8, 228, 264]
Vitexin	24				~200.3 (1) Apoptosis							[49]
Wogonoside		Apoptosis			Apoptosis							[37]
FLAVANOLS												
Catechin	48 96	>100 (1) >34.5 (1)					>2756.1 (1)				>34.5 (1)	[53, 265, 273]
Epicatechin, EC	48 72 96	>100 (1) >31.5 (1)					 >320 (1)	 >200 (1)			 >34.5 (1)	[132, 265, 273, 274]
Epigallocatechin, EGC	48 72	107.7 (1) 97.5 (1) Apoptosis										[230]
Epigallocatechin gallate, EGCG	24 48 72	155.8±24.9 (2) 60.0 (1) 57.5 (1) Apoptosis	>50 (1) Apoptosis		>50 (1) Apoptosis	 ~60 (1)	126.5 (1) 125.0 (1) NA at 20 (1)	378 (1) Apoptosis	272 (1) 16.0±1.6 (1) Apoptosis		30.0 (1)	[48, 69, 72, 105, 198, 230, 231, 244, 275-277]
FLAVONOLS												
Fisetin	48 96	 Apoptosis			32 (1) Apoptosis		15±2 (1) 62.9±3.4 (2) Apoptosis					[74, 132, 261, 262, 270]
Galangin	48 72 96	 43 (1) Apoptosis	 35 (1)		31.5 (1) 125 (1) Apoptosis		12±0.8 (1) 69 (1) 44.3±2.0 (2) Apoptosis	 30 (1)				[8, 74, 132, 161, 261, 262]

(Table 2) contd….

Flavonoids	Time, h	Mean IC_{50} Value ± Standard Error, µM (Number of Published Constants)*										References
		HL-60	NB4	KG1a	U937	THP-1	K562	Jurkat	CCRF-CEM	MOLT-3	MOLT-4	
Kaempferol	24 48 72 96	125±20 (1) 42.1 (1) 30 (1) 10.8 (1) Apoptosis			NA to 175 (1)		NA to 175 (1) 98.7±11.2 (1) Apoptosis	~50 (1) 48.2±2.4 (1) Apoptosis	NA to 175 (1)		9.8 (1)	[112, 132, 243, 260, 265, 274, 278, 279]
Morin	24 48 96	250.0±40.0 (1) 7.94 (1) Apoptosis			~250 (1) Apoptosis		>320 (1)				11.6 (1)	[132, 169, 232, 243, 265]
Quercetin	24 48 72 96	85.2±29.7 (6) 45.9±5.7 (6) 40.8±10.0 (4) 7.7 (1) Apoptosis	Apoptosis	155 (1) Apoptosis	32.3±24.3 (2) Apoptosis	37 (1) Apoptosis	40.0±7.0 (2) 10±2 (1) 31.4±10.3 (4) 64.1±5.1 (2) Apoptosis	32.8±22.8 (2) 35.7±28.7 (3) Apoptosis	79.2 (1) Apoptosis	10 (1) Apoptosis	29.9 (1) >33.1 (1) Apoptosis	[10, 31, 55, 74, 82, 85, 92, 97, 107, 112, 132, 136, 153, 159, 162-164, 172, 179, 194, 199, 233, 243, 244, 262, 265, 274, 280-284]
O-methylated flavonols												
Casticin	24 48 72	0.9±0.2 (3) 2.6±2.2 (2) Apoptosis			1.0±0.1 (1)		5.95 (1) Apoptosis		0.3±0.0 (1)			[21, 103, 105, 168]
Tamarixetin	72	7.5±1.6 (1) Apoptosis			5.5±2.0 (1) Apoptosis		24.1±5.1 (1)			7.5±2.4 (1)		[162]
Flavonol glycosides												
Quercitrin	8	NA to 80 (1)										[125]
Rutin	8 48 72 96	NA to 80 (1) 105±82.1 (2)					897±43.0 (1) >640 (1) Apoptosis					[85, 107, 123, 125, 132]
Tiliroside	48 72				NA to 84.1(1)		NA to 84 (1)	11.6±2.6 (1)	28.8 (1) NA (1)			[105, 274, 278]
FLAVANONES												
Eriodictyol	24 48 72	35.0±3.0 (1) Apoptosis			>100 (1) >100 (1) >100 (1)							[179, 221, 269]

(Table 2) contd….

Flavonoids	Time, h	Mean IC_{50} Value ± Standard Error, μM (Number of Published Constants)*										References
		HL-60	NB4	KG1a	U937	THP-1	K562	Jurkat	CCRF-CEM	MOLT-3	MOLT-4	
Flavanone	72 96	45 (1)					55.1±4.0 (2) Apoptosis					[113, 132, 262]
Naringenin	24 48 72 96	700±100 (1) 185.3±32.3 (2) >200 (3) NA to 100 (3) Apoptosis	138 (1)		190±50 (1) 160 (1) Apoptosis	NA to 80 (1) >100 (1) >100 (1) Apoptosis	75±6 (1) >200 (2) 291.9±8.2 (2) Apoptosis	206±50 (1) >200 (1) >100 (1)			>36.7 (1)	[8, 18, 45, 74, 132, 134, 139, 154, 157, 175, 179, 182, 207, 243, 265, 285]
O-methylated flavanones												
Hesperetin	24	500±100 (1) Apoptosis				NA to 80 (1)						[182, 243]
Flavanone glycosides												
Hesperidin	24 72	NA to 80 (1)						>200 (1)				[182, 274]
Naringin	24 48 96	NA to 80 (1)			NA to 500 (1)	>400 (1)	>640 (1)					[132, 139, 182]
ISOFLAVONES												
Daidzein	96	>39.3 (1)	NA at 50 (1)								>39.3 (1)	[239, 265]
Genistein	24 48 72 96	31.5 (1) 21.2±8.4 (3) 31.2±8.7 (4) 10.5±10.5 (2) Apoptosis	18 (1) Apoptosis	23 (1)	>100 (1) 47.1±24.9 (2) 40.5±7.5 (2)		37.5 (1)	23 (1) Apoptosis	17.3±0.7 (1) Apoptosis	12.7 (1)	48.1 (1) 10.6 (1)	[8, 196, 205, 224, 235, 236, 238, 239, 251, 265, 269, 286]
O-methylated isoflavones												
Glycitein	48	84.4 (1)			103.5 (1)							[224]
Tectorigenin	48	22.3 (1) Apoptosis			28 (1)							[224]
Isoflavone glycosides												
Glycitin	48	>200 (1)			>200 (1)							[224]
Tectoridin	48	>200 (1)			>200 (1)							[224]

*Cytotoxic activities measured by counting of cells, measuring cellular viability by XTT, MTT, MTS, WST-1, sulforhodamine (SRB), neutral red, Alamar Blue or ATP cell viability assay or by incorporating [^{3}H]-thymidine into replicating DNA; NA, not active.

in HL-60, U937, THP-1, K562 and Jurkat cells compared to KG1a and CCRF-CEM cells, as indicated in (Table **2**), and reviewed in [10, 142, 223, 224]. Thus, no single flavonoid is cytotoxically equally active in all cell lines making it needful to select specific polyphenolic compounds for different types of leukemia [10]. Moreover, longer-term exposure can in turn produce some heterogeneity in antileukemic responses as observed by treating HL-60 cells with kaempferol, as indicated in (Table **2**), and described elsewhere [225].

The important role of cellular context in antileukemic properties is supported by analyzing the growth inhibitory effects of flavonoids in cells at various differentiation degrees [115, 226]. It has been indeed reported that cytotoxic action of casticin depends on the maturation stage of HL-60

cells. Monocytic differentiation of these cells induced by 12-O-tetradecanoylphorbol-13-acetate (TPA) or 1α, 25-dihydroxyvitamin D3 (1,25 (OH) 2D3) leads to emergence of resistance to casticin showing that cells with less differentiated phenotypes are more sensitive to this flavonoid compared to the differentiated ones [21].

On the other hand, it is clear that antileukemic action of flavonoids depends also on the molecular structure of polyphenols and even minor structural modifications may strongly affect their cytotoxic properties [8, 10, 120, 184]. Although it is agreed that antiproliferative effects of flavonoids cannot be predicted just on the basis of their composition, some structural elements are still observed as activity requisites, including the presence of C2-C3 double bond and free hydroxyl groups [118, 135, 185]. Indeed, it has been shown in several leukemia lines that luteolin with hydroxyl groups in 3` and 4` positions of the B ring is generally more potent than apigenin possessing only 4` hydroxyl group. Both compounds are in turn cytotoxically stronger compared to chrysin without any free hydroxyl groups in the B ring of flavone backbone, as indicated in (Table **2**), and described elsewhere [10, 90, 140].

One important characteristic of flavonoids can be related to their O-methylation as methoxyflavonoids generally exhibit stronger cytotoxic activity than non-methoxylated flavonoids [227]. This feature becomes evident considering the activities of some O-methylated flavonoids bearing different numbers of methoxyl groups in their diphenylpropane (C6-C3-C6) skeleton, such as eupatorin [216], wogonin [193, 228], casticin [21, 109, 111, 174], or tamarixetin [168] (Table **2**).

Another important structural trait of flavonoids associated with significant changes in their anticancer properties includes glycosylation. It is suggested that flavonoids with glycosidic substitutions at A and/or C ring are much less effective than respective aglycones, regardless of certain substitution position or composition of sugar moiety [138, 197]. It remains to be determined whether this phenomenon is caused by the complicated penetration of glycosides through cell membrane or the glycosides are inactive due to the steric hinderance of glycosidic moiety [197, 229]. The data compiled in (Table **2**) confirm this statement in general terms, as vitexin (apigenin-8-C-glucoside) exerts lower antiproliferative activity than apigenin towards U937 cells [53] and homoorientin (luteolin-6-C-glucoside) is cytotoxically less potent than luteolin in HL-60 cells [230]. Also, the glycosylation of quercetin producing rutin (quercetin-3-O-rutinoside) or quercitrin (quercetin-3-O-rhamnoside) brings along a significant decrease in growth inhibition of HL-60 cells and attenuates proapoptotic activity of the respective aglycone [91, 131, 231]. In different leukemia cell lines (HL-60, U937, THP-1), cytotoxic effects of flavanone aglycones eriodictyol, naringenin and hesperetin are considerably weakened by addition of glycoside moiety to these molecules generating eriocitrin (eriodictyol-7-O-rutinoside), naringin (naringenin-7-O-neohesperidoside) and hesperidin (hesperetin-7-rutinoside), respectively [145, 163, 188, 229]. Also, genistein and tectorigenin are significantly more potent antileukemic agents compared to their inactive glycosides genistin (genistein-7-glucoside) and tectoridin (tectorigenin-7-glucoside) in HL-60 cells [232]. Despite these representative examples, there are still some important exceptions of this general rule as aglycone baicalein and its glycoside baicalin (baicalein-7-O-glucuronide) display rather comparable antiproliferative and apoptogenic activities in different leukemia cells [233-235]. Also, scutellarin (scutellarein-7-glucuronide) is similarly or even more active than the respective aglycone scutellarein [236]. Moreover, kaempferol glycoside tiliroside seems to be a therapeutically interesting compound exhibiting higher cytotoxic potency than kaempferol towards T-lymphoid leukemia cell lines Jurkat and CCRF-CEM (Table **2**).

The data presented in (Table **2**) also demonstrate that compared to other subclasses of flavonoids, i.e. flavones, flavonols or isoflavones, various flavanones (including eriodictyol, naringenin and hesperetin) display only modest cytotoxic activity in different leukemia cells [8, 18, 140, 160, 214]. This tendency can indicate the importance of the C2-C3 double bond (which is absent in flavanones) in flavonoid backbone for expression of stronger antiproliferative and apoptosis-inducing activity [8, 138]. In addition to the absence of C2-C3 double bond, the lack of another favorable structural requisite for antileukemic activity, i.e. the C4 carbonyl in A ring [138] makes the cytotoxic potency of several flavanols rather limited, as shown in (Table **2**), and described eslewhere [57, 204, 237, 238]. This conclusion arouses some suspicion in general suggestion about the protective role of green tea components against leukemia [7]. However, it is still possible that some other constituents, including theaflavins, can also contribute to the chemopreventive properties of green tea against the development of hematological malignancies [239]. Despite the promising antileukemic properties of several natural flavonoids as presented in (Table **2**), the efficacy of these polyphenols at rather high concentrations may turn out to be an obstacle for their use *in vivo*, indicating the necessity to apply novel strategies, including synthetic modifications as well as nanotechnological approaches [240].

6.2. Arrest of Cell Cycle Progression by Flavonoids in Human Leukemia Cells

The growth inhibition of cancer cells by flavonoids is highly related to induction of derangements in cell cycle machinery and arresting cycle progression likely contributes to the antileukemic effects of natural polyphenols. The overview of current knowledge about blocking cell cycle progression through different phases by different flavonoids is presented in (Table **3**). It can be seen that induction of cell cycle arrest is cell type-specific event being determined by various cell internal environments and expression of diverse molecular targets, but depends also on the structure of a specific flavonoid, its doses and treatment times [10, 118, 134]. Data in (Table **3**) clearly indicate that flavonoids appear to cause an accumulation of leukemic cells mainly in G2/M and G0/G1 phases; however, some treatments induce also S phase arrest.

The most intensely studied flavonoid quercetin can cause an increase in cells in G2/M phase in both myeloid and lymphoid leukemia lines (HL-60, U937, K562, Jurkat, MOLT-3, MOLT-4), while inducing G0/G1 phase arrest only in mye-

Table 3. Arrest of cell cycle progression by flavonoids in human leukemia cell lines.

Cell Line	Blockade of Cell Cycle Progression in Different Phases by Different Flavonoids			References
	S Arrest	G2/M Arrest	G0/G1 Arrest	
HL-60	Baicalein, chrysin, kaempferol, tangeretin	Apigenin, apigetrin, baicalein, baicalin, casticin, eupatorin, genistein, kaempferol, morin, quercetin, tamarixetin, tangeretin	Apigenin, genistein, oroxylin A, quercetin, wogonoside	[10, 38, 40, 77, 109, 117, 118, 150, 168, 175, 212, 216, 220, 225, 241, 243, 248, 254, 261, 275]
NB4		Genistein		[117, 247]
KG1a	Apigenin		Chrysin, quercetin	[10]
U937		Eupatorin, quercetin, tamarixetin	Apigenin, chrysin, oroxylin A, wogonin, wogonoside	[10, 16, 38, 40, 168, 216, 242]
THP-1		Apigenin, wogonin	Chrysin, quercetin	[10, 228]
K562	Apigenin	Apigenin, apigetrin, casticin, flavanone, flavone, fisetin, 3-hydroxyflavone, luteolin, quercetin, tangeretin	Chrysin, fisetin, galangin, naringenin, quercetin, wogonin	[10, 19, 23, 49, 70, 76, 80-82, 134, 138, 174, 206]
Jurkat	Apigenin, genistein, quercetin	Genistein, 3-hydroxyflavone, quercetin	Chrysin	[10, 98, 103, 198, 245, 246]
CCRF-CEM	Quercetin	Genistein	Apigenin, baicalin, chrysin	[10, 235, 244]
MOLT-3	Apigenin	Eupatorin, quercetin	Chrysin	[10, 216]
MOLT-4	Quercetin, tangeretin	Quercetin	Nobiletin	[159, 252]

loid cells (HL-60, KG1a, THP-1, K562) and S phase arrest only in lymphoid cells (Jurkat, CCRF-CEM, MOLT-4), as indicated in (Table **3**), and described elsewhere [10, 76, 80, 98, 134, 138, 159, 198, 200, 206, 220, 241, 242]. Another abundantly occurring flavonoid, apigenin, is also a potent suppressor of cell cycle progression in various leukemia models stopping cells in S, G2/M and/or G0/G1 phases, depending on the certain cell line [10, 18, 150], as mentioned in (Table **3**). However, treatment with chrysin progressively increases the leukemia cells mainly in G0/G1 phase [10, 80], while genistein blocks the cell cycle predominantly in G2/M phase, as noted in (Table **3**) and described in [117, 212, 243-247]. It is still needful to bear in mind that the phase of certain cell cycle arrest induced by a specific flavonoid can also depend on the drug concentration and exposure time, as demonstrated in treating MOLT-4 cells with quercetin [200], HL-60 cells with kaempferol [225] or Jurkat cells with genistein [246].

As various flavonoid aglycones induce the cell cycle arrest in different phases, their glycosylated analogues seem to be able to cause the blockade only in G2/M (apigetrin, baicalin) or G0/G1 phase (baicalin, wogonoside) [19, 40, 235, 248), as seen in (Table **3**). Moreover, it is important to point out that no data about the distinct cell cycle arrests can be found for treatment of human leukemia cells with flavanols, reflecting the limited growth inhibitory activities of these green tea polyphenols in established cell lines derived from various types of hematological malignancies, at least in those observed in the current study.

6.3. Differentiation-inducing Potency of Flavonoids in Human Leukemia Cells

Due to the deficiencies in normal cellular differentiation processes, accumulation of immature blasts is a typical characteristic for hematological malignancies. In recent years, increasing evidence has demonstrated that several flavonoids possess the ability to induce differentiation of various leukemia cells making these natural compounds attractive candidates for antileukemic therapy [20, 70]. Although the knowledge about differentiation inducing effects of flavonoids is still rather limited, the currently known data are summarized in (Table **4**). These data reveal that differentiation pathway induced by flavonoids depends largely on the specific cell line, but also on structural peculiarities of certain polyphenols [160]. Therefore, it can be supposed that similarly to antiproliferative activity, also the differentiation inducing effects of flavonoids can probably not predicted on the basis of chemical composition and structure, meaning that each compound should be investigated systematically in different leukemia cells in order to gain insight into their individual potencies.

It is important to point out an interesting distinctive feature in differentiation inducing properties of flavonoids: whereas glycosylation of apigenin leads to the loss of cytotoxic potency (Table **2**), both apigenin and apigetrin are able to cause erythrocytic differentiation in pluripotent K562 cells indicating that the glycoside moiety plays no determining role in the induction of cellular differentiation [18, 19]. Apigetrin can also trigger granulocytic differentiation in HL-60

Table 4. Flavonoids as differentiation inducers of leukemic cells.

Flavonoid	Cell Line	Differentiation Pathway	References
FLAVONES			
Apigenin	HL-60	Granulocytic	[160]
	K562	Erythrocytic	[18]
Chrysin	K562	Erythrocytic	[18]
Flavone	K562	Erythrocytic	[18]
Luteolin	HL-60	Granulocytic	[160]
Tricetin	HL-60	Monocytic	[120]
Chrysoeriol	HL-60	Monocytic	[120]
Diosmetin	HL-60	Monocytic	[120]
Oroxylin A	HL-60	Monocytic	[38]
	U937	Monocytic	[38]
Wogonin	HL-60	Granulocytic	[73]
	NB4	Granulocytic	[73]
	U937	Granulocytic	[16, 73]
	K562	Erythrocytic	[37]
Apigetrin	HL-60	Granulocytic	[77]
	K562	Erythrocytic	[18, 19]
Baicalin	HL-60	Differentiation	[248]
Wogonoside	HL-60	Monocytic	[40]
	U937	Monocytic	[40]
FLAVONOLS			
Galangin	K562	Monocytic	[80]
Quercetin	HL-60	Monocytic	[160]
	K562	Erythrocytic	[76]
ISOFLAVONES			
Genistein	HL-60	Granulocytic and monocytic	[117, 160, 232, 278]
	NB4	Granulocytic	[117, 247]
Tectorigenin	HL-60	Granulocytic and monocytic	[232]

cells [77], similarly to the respective aglycone apigenin [160]. In addition, another flavone glycoside, wogonoside, is able to promote differentiation of HL-60 and U937 cells; however, differently from the granulocytic maturation caused by aglycone wogonin, wogonoside induces differentiation of these myeloblastic leukemia cells along monocytic pathway [16, 40, 73] (Table **4**). These data indicate that glycosidic substitutions in flavonoid backbone could probably not attenuate their differentiation inducing abilities; however, further evidence is certainly needed to confirm this conclusion.

Isoflavones, genistein and tectorigenin, are still the only flavonoids promoting differentiation of HL-60 cells along both granulocytic as well as monocytic pathways, as shown in (Table **4**), and described eslewhere [160, 232]. In contrast, flavanone naringenin possesses no differentiation inducing ability neither in K562 nor HL-60 cells, even at high doses [18, 160]. Moreover, there are still no data about the possible differentiation promoting effects of flavanols in any leukemia cells; however, this knowledge would be highly needed considering the discrepancy between limited cytotoxicity of these polyphenols and general belief in the antileukemic potency of green tea constituents.

6.4. Antileukemic Activity of Flavonoids in Chemoresistant Human Leukemia Sublines

Development of multidrug resistance during chemotherapy has remained a major obstacle for successful cancer treatment being often correlated to the overexpression of membrane-associated transporters, which pump out various anticancer agents from target cancer cells [28, 96, 125, 249]. The best known of these efflux proteins is P-glycoprotein (permeability glycoprotein [P-gp], also known as multidrug resistance protein [MDR1], or ATP-binding cassette subfamily B member 1 [ABCB1], or cluster of differentiation 243 [CD243]) and its overexpression is associated with the MDR phenotype [65, 250]. It is rather common that tumor cells resistant to any drugs may exhibit cross-resistance also to the others [81]. Therefore, it is highly needed to find new effective strategies to overcome the chemoresistance and discover novel agents with cytotoxic potency in chemoresistant cells. In recent years, flavonoids have come forth as attractive candidates for treatment of drug-resistant malignancies.

Data about the growth inhibitory effects of flavonoids in different chemoresistant sublines of human leukemia cells are presented in (Table **5**). The relative resistance (risk ratio, RR) to standard chemotherapeutics (RR, defined as the ratio of IC_{50} values of a compound in resistant subline and its sensitive parent line) is often very high showing an extensive decrease in sensitivity of leukemia cells to the respective drugs. However, relative resistance of several flavonoids in these cells is closed to one revealing similar (RR~1) or even higher (RR<1) cytotoxic efficiency in chemoresistant sublines compared to their parent lines (Table **5**).

The most widely studied flavonoid quercetin is active in chemoresistant sublines of different leukemia cells possessing even stronger antileukemic efficacy in anthracycline-resistant HL-60 cells, doxorubicin-resistant K562 cells and daunorubicin-resistant MOLT-4 cells than in the respective parent lines [88, 251, 252] (Table **5**). Also, the O-methylated quercetin, tamarixetin, exerts a~1.3-fold higher cytotoxic potency in doxorubicin-resistant K562 cells than in its parent line [168]. While apigenin may possess some therapeutic potential in Imatinib-sensitive as well as Imatinib-resistant CML (K562) cells [81], wogonin is able to induce also erythrocytic differentiation of both these lines providing a possible alternative for treatment of this type of leukemia [70]. Two flavonols, kaempferol and casticin, display significant growth inhibitory effects in CCRF-CEM and its multidrug-resistant subline CEM/ADR5000; whereas considering the activity of casticin at very low micromolar doses, this compound might be a possible candidate agent to treat T lymphoblastoid leukemia [111, 253]. Several polymethoxyflavones are able to suppress the growth of another lymphoblastoid leukemia line MOLT-4 and its daunorubicin-resistant cells, revealing almost equal or even stronger activity in chemoresistant cells, as seen in (Table **5**), and described in [252]. Although rather limited, these results could probably lead to the development of novel and more targeted therapies for chemoresistant leukemias, improving thus the current arsenal of strategies used to fight against hematological malignancies.

7. SELECTIVITY OF CYTOTOXIC ACTION OF FLAVONOIDS TOWARDS MALIGNANT BLOOD CELLS

Besides drug resistance, another serious problem emerging during chemotherapy is related to the harmful side effects limiting the overall efficacy of treatment. Indeed, most clinically used anticancer agents reveal a broad spectrum of nonspecific activities [213]. Therefore, an important criterion for development of novel anticancer agents involves the selectivity towards malignant cells [2, 185]. The current knowledge about action of flavonoids in different normal blood cells is summarized in (Table **6**). These data clearly demonstrate that blood cells derived from healthy volunteers are much less sensitive to flavonoids compared to the different leukemia cell lines [10]. Indeed, no or only a very small cytotoxic activity even at high doses of several flavonoids in normal hematopoietic and mature blood cells further suggests the potential application of these plant secondary metabolites as novel antileukemic agents [21, 25, 37, 49, 55, 72, 134, 149, 198, 218, 224, 254-259) (Table **6**). It becomes evident that flavonoids tend to preferentially act in fast-growing malignant cells while leaving normal counterparts mostly unaffected or even exerting some cytoprotective effects on healthy cells [25, 49, 189, 192, 244]. Taken together, specific cytotoxicity of several flavonoids towards leukemia cells makes these natural polyphenolic compounds attractive agents for both chemopreventive and/or chemotherapeutic strategies against leukemia.

CONCLUSIONS AND FUTURE PERSPECTIVES

In this comprehensive review, we demonstrate a great potential of natural flavonoids in development of novel drugs against hematological malignancies encouraging further studies to delineate their possible application in future clinical treatment schemes. Although the exact cellular mechanisms triggered by these polyphenols have largely remained elusive and identification of molecular targets still lies ahead, it is evident that combination of growth inhibitory, cell cycle arresting, apoptosis promoting, and differentiation inducing activities make flavonoids attractive candidates for treatment of leukemia. Due to their cytotoxic properties, several flavones like apigenin, baicalein, luteolin, wogonin and baicalin, but also some flavonols, such as quercetin, casticin and tamarixetin, and isoflavones genistein and tectorigenin show a clear promise as chemopreventive or chemotherapeutic agents against different types of leukemia.

However, despite these promising results and attractive perspectives to incorporate flavonoids in future therapeutic options, there are still some obstacles needed to overcome. First, the antileukemic effects observed in established cell lines do not always reflect the action of these compounds in primary samples derived from patients [38, 157]. Moreover, *in vitro* chemosensitivity data could not always predict *in vivo* activity of a compound and thus, *in vitro* results could not give a direct promise for *in vivo* efficacy [233, 235]. Nevertheless, established human cell lines still provide valuable tools for studies of carcinogenic mechanisms and possibilities to interfere with different neoplastic changes. Moreover, it has been reported that quercetin can induce similar or even stronger cytotoxic effects in malignant blood cells

Table 5. Effect of flavonoids on chemoresistant leukemia cell lines.

Cell Line	Chemoresistant Subline	Relative Resistance (RR)* to Chemotherapy Drugs	Relative Resistance (RR)* to Flavonoids	References
HL-60	HL-60, R; anthracycline-resistant	Doxorubicin 328 Epirubicin 72 Daunorubicin 1367 Mitoxantrone 3700 Vincristine >5900	Quercetin **0.50** Morin 1.12	[251, 261]
K562	K562/adr; doxorubicin-resistant		Quercetin **0.45**	[88]
	K562/A; doxorubicin-resistant	Doxorubicin 56.94	Quercetin 2.59	[59]
	K562/ADR; doxorubicin-resistant		Quercetin 1.24	[206]
	K562/ADR; doxorubicin-resistant		Quercetin 1.02 Tamarixetin **0.77**	[168]
	K562/IMA3; Imatinib-resistant	Imatinib >50	Apigenin 4.06 (48 h) Apigenin 25.20 (72 h)	[81]
	K562-R; Imatinib resistant		3-Hydroxyflavone 1.22	[23]
	K562/sti; Imatinib-resistant	Imatinib 125.00	EGCG 1.12	[78]
CCRF-CEM	CEM/ADR5000; multidrug-resistant	Doxorubicin 1036 Vincristine 613 Paclitaxel 200	Kaempferol **0.73**	[253]
	CEM/ADR5000; multidrug-resistant	Doxorubicin 1036 Epirubicin 484 Vincristine 613 Docetaxel 438 Paclitaxel 200	Casticin 1.57	[111, 262]
MOLT-4	MOLT-4/DNR; daunorubicin-resistant	Daunorubicin 13.76	Baicalein 1.38 Nobiletin **0.60** Tangeretin **0.51** Wogonin **0.96** EGCG 1.03 Quercetin **0.94**	[252]

*Relative resistance (RR) is defined as the ratio of IC_{50} values of a compound in resistant subline and sensitive parent cells.

Table 6. Effects of flavonoids in human normal blood cells.

Flavonoids	Cellular System*	Time, h	Activity Data; Mean IC_{50}, µM	References
FLAVONES				
Acacetin	PBMC	24	>100	[126]
Apigenin	$CD34^+$ stem progenitors from cord blood	24	>500	[10]
	PBL	24	>200	[150]
Baicalein	Peripheral blood cells	96	>100	[263]
	Myeloid cells	96	>100	[263]
Chrysin	$CD34^+$ stem progenitors from cord blood	24	>200	[10]
Luteolin	PBL	72	340.1	[264]
Nobiletin	PMN	24	NA at 100	[265]
Tangeretin	PMN	24	NA at 100	[265]
Wogonin	Peripheral blood T cells	24	NA at 100	[213]
	PHA-stimulated peripheral blood T cells	24	NA at 100	[213]
Baicalin	PBMC	132	>900	[266]
Scutellarin	PBMC	24	NA at 5-10	[236]

(Table 6) contd….

Flavonoids	Cellular System*	Time, h	Activity Data; Mean IC_{50}, μM	References
FLAVANOLS				
Epicatechin, EC	PBMC	72	NA at 200	[267]
EGCG	PBMC	48	NA at 200	[78]
	PBL	72	NA at 6.5-19.6	[268]
FLAVONOLS				
Kaempferol	PBMC	72	NA at 200	[267]
Quercetin	$CD34^+$ stem progenitors from cord blood	24	>500	[10]
	PBMC	24	NA at 10-20	[33]
	PBMC	48	NA to 33.1	[206]
	PBMC	72	NA at 200	[267]
Casticin	PBMC	24	NA to 2.7	[21]
Tiliroside	PBMC	72	NA at 200	[283]
FLAVANONES				
Naringenin	PMN		NA to 400	[49]
	PMN	24	NA to 80	[188]
Hesperetin	PMN	24	NA to 80	[188]
Hesperidin	PBMC	72	NA at 200	[267-270]
ISOFLAVONES				
Genistein	PBMC	72	51.4±15.2	[244]

* PBL, peripheral blood lymphocytes; PBMC, peripheral blood mononuclear cells; PHA, phytohemagglutinin; PMN, polymorphonuclear leukocytes; NA, not active.

isolated from patients compared to its activity in cultured human leukemia cell lines [31, 224]. It is clear that to turn from speculations to therapeutic application, further investigation is urgently needed involving animal studies as well as justified and well-designed clinical trials. Some recent works with animal models show that flavonoids can exhibit different antileukemic effects in murine xenografts *in vivo* [1, 9, 51, 260]. However, it is clear that much research is still ahead. After all, interindividual differences in antileukemic responses to flavonoids still remain possible and unpredictable [271-295].

Although it is generally accepted that cytotoxic action of flavonoids is selective towards malignant cells, knowledge about other possible effects of these polyphenolic compounds in healthy cells is still rather scarce. It has been indeed shown that quercetin can suppress some normal immune functions by inhibiting the activation of T cells, restraining thus the prospects of its use in clinical settings [55]. Finally, it is well known that flavonoids exist naturally in combinations but there is still little information available about their possible synergistic or antagonistic interactions. It is likely that individual flavonoids can either enhance or negate the anticancer effects of other polyphenols providing thus an immense amount of new possibilities for studies of combined antileukemic activities [295-300].

LIST OF ABBREVIATIONS

ALL = Acute lymphocytic leukemia

AML = Acute myelogenous leukemia

ATRA = All-trans retinoic acid

ABCB1 = ATP-binding cassette sub-family B member 1

CLL = Chronic lymphocytic leukemia

CML = Chronic myelogenous leukemia

CD243 = Cluster of differentiation 243

MMP = Matrix metalloproteinase

MDR1 = Multidrug resistance protein

ROS = Reactive oxygen species

TPA = Tetradecanoylphorbol-13-acetate

VEGF = Vascular endothelial growth factor

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflict of interest.

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