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Review article

Plant-derived natural compounds as promising anticancer agents in hematological malignancies

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Abstract

The latest treatments have improved outcomes for patients with hematological malignancies, but relapse, treatment resistance and particularly side effects still remain as common limitations of these treatments. Given the disadvantages of the existing conventional therapeutic methods, developing more effective drugs with less toxicity and side effects is of paramount importance. Medicinal herbs have historically proven their worth as a pool of potential therapeutic agents for leukemia and lymphoma, and today they still represent a rich source for the recognition of new drug leads. The role of the positive synergistic effects of plant-derived natural products and common chemotherapeutic drugs is also considered as one of the rational reasons for paying attention to the medicinal plants in recent chemoprevention and chemotherapeutic investigations. Noteworthy, targeted delivery of plant-derived natural products via the incorporation of nanoparticles or antibodies would be a major step to improve their bioavailability and then to increase their therapeutic effects. In this study, we reviewed plant-derived agents approved and/or under investigation for hematological malignancies.

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1. Introduction:

Leukemia and lymphoma are now curable in many cases due to the enormous improvements in the efficacy of chemotherapeutic drugs, however, significant adverse effects and chemoresistance have led to treatment failure and early relapse (1-4). Given the challenges of the existing conventional treatment methods, developing novel and potent agents with less toxicity and side effects is one of the most important requirements in cancer treatment research. Despite the power of synthetic chemistry as an appealing field to discover and develop new therapeutic agents, the bioactive plant extracts

and their derivatives would be very worthwhile for detecting efficient and safe anti-tumor therapeutics (7, 8). American-Indians were the first to use extracts from the roots of mayapple, Podophyllum peltatum, as an effective treatment for skin cancers. The main constituent, podophyllotoxin, was the forerunner of the group of anticancer agents known as the podophyllins (9). Natural products have been used as traditional medicines throughout human history. Nowadays, about one-third of the common pharmaceuticals are natural products or their derivatives (10-12). Not only are a large number of chemotherapeutic agents derived from plants also many naturally occurring substances present in the plants have been identified as potential chemopreventive agents. Today, more researchers have focused on the utilization of phytochemicals such as curcumin, genistein, resveratrol, epigallocatechin-3-gallate, and sulforaphane for managing cancer (13-17). Additionally, the role of positive synergistic effects of secondary metabolites and chemo drugs should not be ignored as one of the rational reasons for paying attention to plant extracts in recent chemotherapeutic and chemoprevention investigations (18).

Despite the fact that natural products have been a rich source of compounds for drug discovery, their use has diminished in the past two decades in part because of technical barriers to screening them in high-throughput assays against molecular targets (19, 20). In some cancers, targeted therapies have greatly delayed tumor progression, and/or improved the life expectancy of patients. However, the vast majority of common cancers were found to be dependent not on a single "targetable" oncogenic activation. It is necessary to say that different types of leukemia and lymphoma are also shown to activate multiple adaptive mechanisms that either cause primary resistance to targeted drugs or help acquired resistance after only a few months of treatments (21). In spite of the predominant industrial focus on synthetic compound libraries, natural products still represent a valuable source for drug discovery given their described by Atanas G. Atanasov (22). Here, we review the history of and latest clinical findings on plant-derived agents (alone and/or in combination with other anticancer drugs) used or under investigation for patients with hematologic malignancies.

2. Anti-leukemic medicinal herbs and their derivatives

2.1. Chemopreventive agents

In general, cancer chemoprevention focuses on the identification of agents that specifically impact the early stages of cellular transformation (23, 24). Plant-derived phytochemicals have been found to have a wide range of anticancer activities in different stages of carcinogenesis, namely cancer initiation, proliferation, and progression (25). An extract derived from Leguminosae (Cassia quinquangulata Rich) was identified as a chemopreventive agent. Then, resveratrol was identified as its active component on the basis of bioassay-guided fractionation (15). In vitro and in vivo studies show that resveratrol by targeting cyclooxygenases (COXs) prevents carcinogenesis and reduce inflammation (15, 26-28). It has been reported that this phytochemical exhibited cytotoxicity in multiple myeloma cell lines through inhibition of NF-κB, Akt, and STAT3 (29). Despite convincing pre-clinical evidence that resveratrol could aid in the treatment of patients with multiple myeloma, a clinical trial found that it caused several severe adverse events, the most prominent of which was renal failure (30). On the other hand, as resveratrol was proven to be safe in a phase II clinical trial, and it did not cause any nephrotoxicity in a phase I study for colorectal cancer patients, this adverse event seemed to be specific to multiple myeloma patients. A few clinical trials have shown that resveratrol has several targets within the cell such as caspase-3, and its efficacy is dependent on the type and stage of cancer, dosage levels, and treatment periods (31).

6-(methylsulfonyl) hexyl isothiocyanate (6-MITC) is another chemopreventive plant-derived product for leukemic that is derived from Wasabia Japonica. One study focusing on the evaluation of anti-leukemic potential of 6-MITC revealed its stronger cytotoxic effects on leukemic cells compared to healthy lymphocytes by inducing apoptosis, and blocking the cell cycle. Interestingly, this compound could induce differentiation of HL-60 cells into granulocytic and macrophage phenotypes (32). In general, despite the scientific importance and potential public health advantage, cancer chemoprevention has not been generally adopted in the clinic. In fact, the delay from the progression of cancer cell transformation to detectable cancer lesions may require years of patient data. However, utilizing malignant chemical biomarkers may illustrate a good way to recognize responses in patients taking phytochemicals.

2.2. Chemotherapeutic agents

2.2.1. Clinically approved agents

Of the 175 small molecules in the area of cancer, 131 (74.8%) are other than synthetic products with 85 (48.6%) actually being either natural products or their derived agents (22). Structures of antileukemic plant-derived agents and their sources were represented in **Fig. 1.** In this section, we will review the plant-derived chemotherapeutic agents which have been approved for therapeutic use for patients with hematological malignancies **(Table 1).**

Vinca alkaloids

Vinblastine and vincristine were first introduced in 1963 and 1965, respectively. They have contributed to long-term remissions and cures patients with childhood leukemia, Hodgkin's lymphoma and many other types of cancer (33, 34) (39). These compounds, known generally as vinca alkaloids, were isolated from the Madagascan periwinkle. Interactions of vinca alkaloids with tubulin, the major component of microtubules in the mitotic spindle, and the subsequent arrest of cells in mitosis (metaphase) are

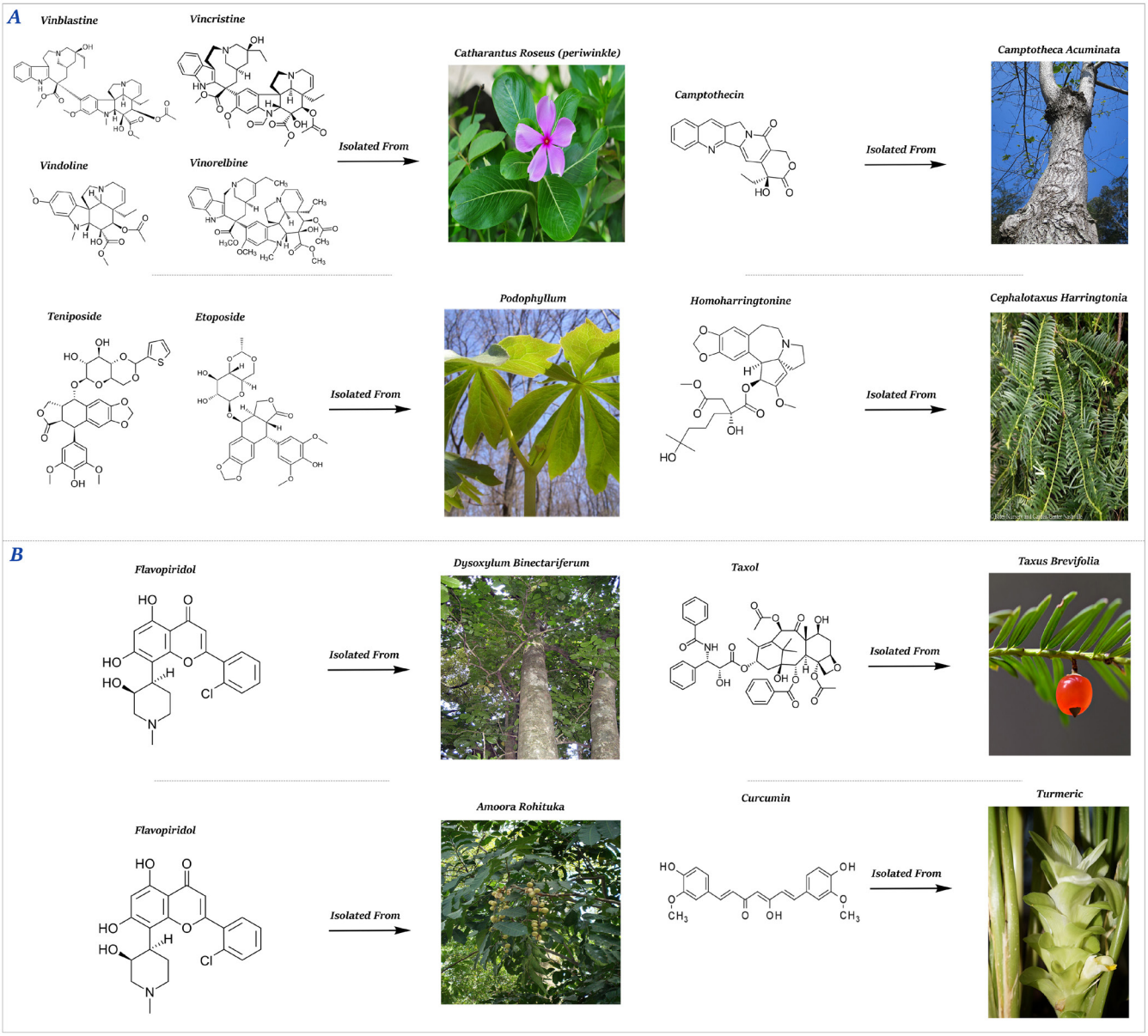

Figure 1: Structures of antileukemic plant-derived agents and their sources. A) Approved agents. B) Agents that are under clinical investigation.

Table 1: Plant-derived natural products approved for therapeutic use in leukemia and lymphoma.

Plant	Traditional use	Anticancer mechanism	Drug	Trade name	Approved by	Introduced	Hematologic malignancies
Catharanthus roseus	Anti-diabetic, anti-malaria and anti-tumor (65, 66)	Microtubule Inhibitor (Microtubule destabilizing)	Vincristine	Oncovin®	FDA	1963	ALL, CML, CLL, MM, HL, NHL
			Vinblastine	Alkaban-AQ®, Velban®	FDA	1965	HL, NHL, CML (blast crisis)
			Vindesine	Eldisine®	FDA	1979	Acute leukemia, lymphoma, HL
			Vinorelbine	Navelbine®	ARMC	1989	HL
			Liposomal vincristine	Marqibo®	FDA	2012	Ph- ALL
Podophyllum genus	Anthelminthic (67)	Inhibitor of topoisomerase II	Teniposide	Vumon®	FDA	1967	ALL, AML, CLL, MM, HL, NHL
			Etoposide	VP-16®	FDA	1980	Relapsed ALL in children
Camptotheca accuminata	Anti-tumor (67)	Inhibition of topoisomerase I	Topotecan	Hycampti®	ARMC	1996	AML, MDS, CML
Cephalotaxus harringtonia	Anthelminthic (67)	Inhibition of protein synthesis	Omacetaxine mepesuccinate (homoharringtonine)	Synribo®	FDA	2012	CML

Abbreviations: ALL, Acute Lymphoblastic Leukemia; **CML,** Chronic myeloid leukemia; **CLL,** Chronic lymphocytic leukemia; **MM,** Multiple myeloma; **HL,** Hodgkin lymphoma; **NHL,** Non-hodgkin lymphoma; **AML,** Acute myeloid leukemia; **Ph⁻ ALL,** Philadelphia chromosome negative acute lymphoblastic leukemia; **MDS,** Myelodysplastic syndrome.

generally accepted as key events in their mechanisms of action. Vinblastine sulfate is currently a component of a number of chemotherapy regimens for the treatment of Hodgkin's lymphoma and is also utilized in the therapy of bladder and breast cancers. Vincristine sulfate is used in various types of chemotherapy regimens for acute lymphoblastic leukemias (ALL) and lymphomas (33, 40). Selective chemical modifications of these two compounds have led to several structural analogues being approved in Europe for cancer treatment. Most notable of these analogous are vinorelbine (41) and vindesine (42, 43). These two compounds are semisynthetic derivatives of vinblastine with current or potential use in treating hematological malignancies (44). These agents are also used in combination with other cancer chemotherapeutic drugs for the treatment of a variety of cancers, including leukemia and lymphoma.

Podophyllotoxin derivatives

Epipodophyllotoxin is the naturally occurring epimer of podophyllotoxin (35) that was isolated as the active anti-tumor agent from the roots of various species of the genus Podophyllum (45). These medicinal herbs possess a long history of medicinal use by early Asian and American cultures, such as the treatment of skin cancers and warts (46). They inhibit topoisomerase II (topo II) and act by interfering with topoisomerase-mediated re-annealing of DNA (single- and double-strand) breaks, especially in the S and G2 phases of the cell cycle followed by accumulation of DNA damage and potent induction of caspase-dependent apoptosis (47). Epipodophyllotoxin is the parent of the two clinically approved agents, etoposide and teniposide (35). Etoposide, etoposide phosphate (a water-soluble prodrug of etoposide), and Teniposide received Food and Drug Administration (FDA) approval in 1983, 1996, and 1993, respectively (48). Etoposide is in regular use for the effective treatment of testicular teratoma and small-cell lung cancer, whereas teniposide has efficacy against ALL and neuroblastoma in children, and non-Hodgkin's lymphoma and brain tumors in adults (9).

Camptothecin

Camptothecin, a cytotoxic pentacyclic alkaloid, was originally isolated from the bark and stem wood of Camptotheca acuminata, a tree indigenous to China in the early 1960s (49). This compound attracted immediate interest as a potential cancer chemotherapeutic agent due to its impressive activity against leukemia and various solid tumors in experimental systems (50). Due to negligible water solubility, this agent was advanced to clinical trials in water-soluble sodium salt form by National Cancer Institute (NCI) in the early 1970s, but it was dropped out of use in the late 1970s because of its lower efficacy and severe bladder- and myelo-toxicity.

Interest in camptothecin subsided for more than a decade (50). Revived attention resulted from the breakthrough discovery of DNA topoisomerase I (topo I) as a therapeutic target for camptothecin. This discovery put camptothecin back on the frontlines of anticancer drug development in the late 1980s (51-53). Not only camptothecin will help to understand the functions of the enzyme topo I_for which it is a

specific inhibitor_but also acts as a lead structure for the design of other molecules that selectively inhibit topoisomerases (54). Chemical manipulation of its structure subsequently produced analogues, including topotecan (Hycamptin) and irinotecan (Camptosar), that have been approved for use in the USA in 1996 (55). Topotecan, but not irinotecan, is used in clinical settings for a wide range of hematologic malignancies such as ALL, acute myeloblastic leukaemia (AML), myelodysplastic syndrome (MDS), and chronic myeloid leukemia (CML).

Homoharringtonine

Another plant-derived agent in clinical use is homoharringtonine that also called Omacetaxine mepesuccinate or Synribo. It is cephalotaxine ester isolated from Cephalotaxus harringtonia var. drupacea (Cephalotaxaceae), which is evergreen coniferous shrubs used in Chinese medicine for the treatment of cancer (56, 57). A racemic mixture of harringtonine and homoharringtonine has also been used successfully in China for the treatment of various types of leukemia. Clinically, purified homoharringtonine exhibits efficient inhibitory effects against AML (58, 59) and CML (60, 61) alone or combined with granulocyte colony-stimulating factor, cytarabine, or interferon-α. In addition, this agent has been reported to produce complete hematologic remission in patients with late chronic phase of CML. Homoharringtonine has been described as an inhibitor of protein synthesis; it inhibits chain elongation during translation by suppressing the substrate binding to the receptor site on the 60S ribosome subunit (62). Efferth et al found that homoharringtonine is more efficient in tumor cells with wild-type p53 in a high-throughput screening assay (with 55 NCI cell lines) (63). A recent study demonstrated that the possible mechanisms of homoharringtonine in myeloma may be the inhibition of Akt phosphorylation and Akt target genes including NF-κB, X-linked inhibitor of apoptosis (XIAP), cellular inhibitor of apoptosis (cIAP), and Cyclin D1 (64). Inhibition of myeloid cell leukemia 1 (MCL1) protein synthesis, and induction of apoptosis were also reported in CML (61).

2.2.2. Agents under clinical investigation

Curcumin

Curcumin is the active compound in the traditional herbal medicine and dietary spice turmeric (Curcuma longa) (68). This yellow spice has a long history of use in traditional remedies of China and India to treat common eye infections, and to treat bites, burns, acne and various skin diseases (69, 70). Curcumin has a surprisingly wide range of beneficial properties, including anti-inflammatory, antioxidant, and anti-cancerous activity (71). This ingredient is one of the most successful compounds investigated in recent years and is currently being assessed as both chemopreventive and chemotherapeutic agent. Curcumin is currently used in human clinical trials for a number of hematological malignancies such as multiple myeloma and MDS and also for a variety of disorders including colorectal cancer, pancreatic cancer, Alzheimer's disease, and psoriasis (25, 72-75). Several attempts combining curcumin with glucuronidation inhibitors such as piperine have also shown promising results to inhibit hepatic and intestinal metabolism (77). It inhibits cancer development and progression by targeting multiple signaling pathways including survival pathways such as those regulated by NF-kB, Akt, and growth factors, extrinsic and intrinsic apoptosis pathways, and last but not least, metastatic and angiogenic pathways (68). Notably, curcumin may also function as a chemosensitizer and enhance the activity of other anticancer drugs, in part by disrupting pathways that lead to treatment resistance (76). It is remarkably non-toxic but exhibits limited bioavailability. Therefore, current research has shifted focus to improving bioavailability to overcome both the variability of absorption and rapid compound metabolism.

Taxol

Among the plant's natural products, Taxol is considered as the undoubted star, which shows efficacy against Kaposi's sarcoma and refractory breast and ovarian cancers. At present, Taxol is the best-selling anticancer agent that reached sales of US $1.5 billion in 2000, which are still growing (78). The complex diterpene Taxol® (Paclitaxel) initially was isolated from the bark of Taxus brevifolia that historically had been used by several Native American tribes for the treatment of non-cancerous conditions. Leaves of T. baccata are also used in Ayurvedic (traditional Asiatic Indian) medicine system, with one reported application for the treatment of cancer (79, 80). Paclitaxel and also several key precursors (the baccatins) exist in the leaves of various Taxus species. Notably, the ready

semi-synthetic conversion of the relatively abundant baccatins to paclitaxel, as well as active paclitaxel analogs such as docetaxel, has provided a major, renewable natural source of this important class of drugs (81). Clinical trials of paclitaxel indicated the potential usefulness of this agent in the treatment of different types of hematological malignancies including ALL, AML, Hodgkin's and non-Hodgkin's lymphoma (Table 2). Unlike vinca alkaloids that destabilize microtubules, Taxol stabilizes them by binding to the beta-tubulin subunits during cell proliferation. Chromosomes are thus unable to achieve a metaphase spindle configuration. This blocks the progression of mitosis and prolonged activation of the mitotic checkpoint triggers apoptosis or reversion to the G0-phase of the cell cycle without cell division. This allows the relationships between structure and activity to be established for hundreds of semi-synthetic analogues, with several more effective analogues being already in clinical trials. This natural product has therefore provided not only a potent drug but also the springboard for next developments (82-84).

Flavopiridol

Flavopiridol or alvocidibis is being investigated for use in leukemia, lymphoma, lung, liver, and esophageal cancers. While flavopiridol is totally synthetic, the basis for its novel structure is the natural product rohitukine isolated from Amoora rohituka and Dysoxylum binectariferum (85-87). Flavopiridol is regarded as a pan-cyclin-dependent kinases (CDK) inhibitor that inhibits multiple CDKs by binding to the ATP-binding pocket of the kinase and then induces cell cycle arrest. Notably, flavopiridol appears to be the most potent agent against the CDK9 pathway which is dysregulated in AML (88). Initial clinical trials using flavopiridol in leukemia and lymphoma were disappointing (89, 90). Byrd and Grever found that the results could be explained by the large difference in protein binding of flavopiridol between fetal bovine serum (as typically used in cell culture) and human plasma. This observation and data from completed trials resulted in designing a schedule of flavopiridol administration with the goal of achieving brief high levels of free drug. Using this new schedule, this group showed that flavopiridol has potent activity in patients with drug-refractory chronic lymphocytic leukemia (CLL) (91). Now, flavopiridol is being evaluated in a multi-center Phase II trial in relapsed/refractory CLL (92) and continues to be investigated in other hematologic malignancies such as AMLs, APL, CML, CLL, SLL, non-Hodgkin lymphoma, diffuse large B cell lymphoma, mantle cell lymphoma, etc. As a snapshot of the current state and perspective for future developments, an overview of advanced plant-derived small chemical entities that are used in clinical trials is presented in **Table 2**. Also, a schematic overview of the main targets of these agents was represented in **Fig. 2.**

3. Synergistic effects of plant-derived and chemotherapeutic agents

Combination therapy has gained momentum in oncology in recent years, with various studies demonstrating higher response rates with combination of drugs compared to monotherapies (113). In fact, the complex synergistic interactions between the drugs and herbs or natural products are supposed to be able to enhance therapeutic effects while reducing toxicity and drug resistance. The FDA recently approved therapeutic combination regimens that illustrated superior efficacy and safety to monotherapies. In addition, the National Cancer Institute has recently highlighted combination therapy as a top research priority in oncology. The major benefit of combinationtherapies is that they reduce the development of drug resistance since cancer is less likely to have resistance to multiple drugs simultaneously. This approach may seem costlier than monotherapy in the short term, but when it is used appropriately, it causes significant savings: lower treatment failure rate, lower case-fatality ratios, slower development of resistance, and fewer adverse effects than monotherapy (114). Since patients treated with doxorubicin that has potent antineoplastic activity over acute leukemia suffer from acute and delayed side effects (115) and also demonstrate acquired drug resistance, a recent study investigated the effect of the combination of doxorubicin and several plants' secondary metabolites (sanguinarine, epigallocatechin-3-gallate, etc.) that modulate multi drug resistance (MDR) on drug-resistant leukemia cells. Notably, combination of nontoxic concentrations of individual natural compound with doxorubicin was shown to significantly sensitize leukemic cells, and significantly enhance the cytotoxicity of doxorubicin (116). Some examples of natural products used in combination with chemotherapeutic drugs that are in phase I-IV clinical trials are summarized in **Table 3.**

Table 2. Plant-derived natural products used in clinical trials for leukemia and lymphoma.

Plant	Traditional use	Lead component(s)	Drug	Other name	Mechanism of action	Hematologic neoplasia	Clinical trial
Curcuma longa	Urinary diseases, diseases of liver, jaundice and cancer (93, 94)	Curcumin	Curcumin	Turmeric Yellow	Anti-inflammatory, anti-oxidative	Maintenance therapy in MM MM T-cell Lymphoma Patients	Phase II Phase II Phase II
Taxus brevifolia	Some non-cancerous conditions and cancer (95)	Paclitaxel	Paclitaxel	Taxol	Microtubule inhibition	Refractory acute leukemia, CML Recurrent and refractory lymphoma	Phase II Phase I/II
			Ortataxel	IDN-5109, BAY-59-8862	Microtubule inhibition	NHL	Phase II
Red grapes	Hyperlipidemia, fatty liver, diabetes, atherosclerosis and aging (96-100)	Resveratrol	Resveratrol	SRT501	Cell cycle arrest and apoptosis	MM	Phase II
Tripterygium wilfordii	Arthritis, muscle and skeletal injury, and skin diseases (101)	Triptolide	Minnelide™ 001	Triptolide O-Methyl	Apoptosis inducing by HSP70	AML	Phase I
Camellia sinensis (Green and white tea)	Flatulence, fever, and diabetes (102, 103)	Catechin	Catechin	Cianidanol	Antioxidant	MM and plasma cell neoplasm	Phase II
Pomegranate	Microbial infection, inflammation, diabetes and cancer (104-106)	Ellagic acid	Ellagic acid	Benzoaric acid	Anti-proliferative, antioxidant	MDS	Phase II
Maclura pomifera	Disease of eye(107)	Morin	Morin	Aurantica	Antiproliferative	AML	Phase I
Amoora rohituka	Microbial infection and diseases of liver (108)	Rohitukine	Alvocidib	Flavopiridol, DSP-2033	CDK9 inhibition	AML CML or Lymphocytic Lymphoma CLL or APL CLL or SLL AML, ALL, or CML CLL or APL Arising From CLL CLL Lymphoma or MM MCL or DLBCL Lymphomas Intermediate-Grade or High-Grade NHL or MCL	Phase I Phase II Phase II Phase I Phase I Phase II Phase II Phase II Phase II Phase I Phase II
			Voruciclib	P1446A	CDK4 and CDK6 inhibition	B-cell malignancy CLL	Phase I Phase I

Abbreviations: MM, Multiple myeloma; **CML,** Chronic myeloid leukemia; **NHL,** Non-hodgkin lymphoma; **AML,** Acute myeloid leukemia; **MDS,** Myelodysplastic syndrome; **CLL,** Chronic lymphocytic leukemia; **APL,** Acute promyelocitic leukemia; **SLL,** Small lymphocytic lymphoma; **MCL,** Mantle cell lymphoma; **DLBCL,** Diffuse large B cell lymphoma.

4. Targeted drug delivery system of medicinal herbs

Targeted drug delivery system refers to a method using different carriers to change the effective components extracted from natural products into agents which can directly concentrate on the target site. This system is an ideal delivery approach and it can reduce the adverse reactions and improve the pharmacological effects [1]. There are different carriers which two of the most important ones used for hematological malignancies are discussed in this review.

4.1. Nanoparticle delivery

The biggest issue with the use of natural products in disease treatment that makes researchers interested in targeted therapy with nanoparticle is their low bioavailability, which has caused problems in clinical trials. Highly lipophilic compounds such as curcumin, resveratrol, and epigallocatechin-3-gallate (EGCG) are not ideal for drug delivery because they do not dissolve well in the bloodstream. These compounds have low bioavailability, and therefore, large quantities of the compounds must be administered in order to achieve

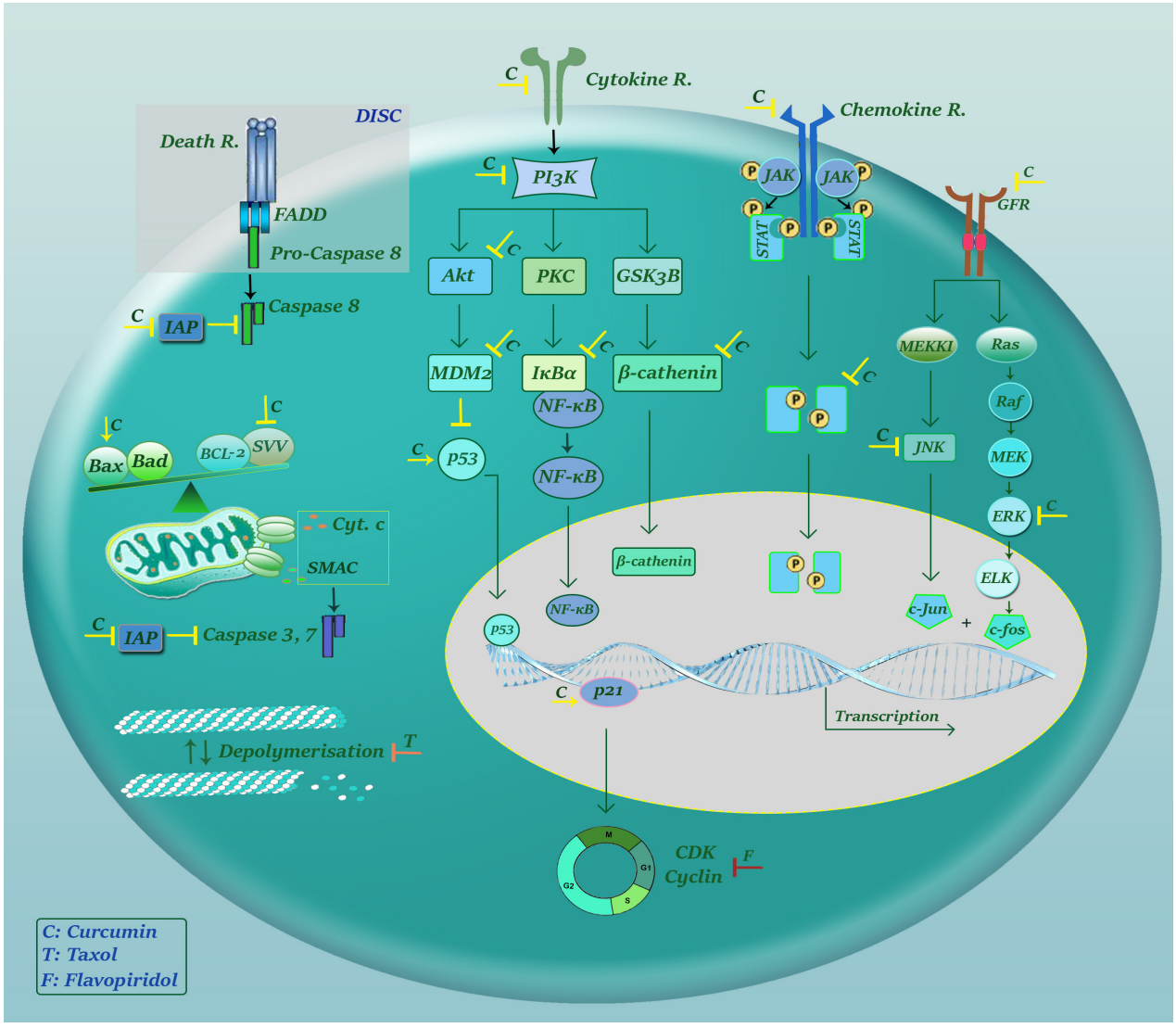

Figure 2: Schematic overview of the main targets of plant-derived natural compounds that are under investigation. Three compounds are shown by C (Curcumin), T (Taxol) and F (Flavopiridol). Curcumin is able to target several mechanisms that are involved in hematological malignancies. It targets several main signaling pathways including Ras/Raf/MEK/ERK pathway, PI3K/Akt pathway, extrinsic and intrinsic apoptosis pathways and JAK/STAT pathway. Taxol stabilizes the microtubule polymer and protects it from disassembly, which in turn blocks the progression of mitosis. Flavopiridol inhibits different cyclins and cyclin-dependent kinases (CDK) and then induces cell cycle arrest and apoptosis. GFR: Growth factor receptor; ERK: Extracellular signal regulated kinase; MEKK1: Mitogen-activated protein kinase kinase 1; JNK: c-Jun N-terminal kinase; JAK: Janus kinase; STAT: Signal transducer and activator of transcription; PI3K: Phosphatidylinositol 3-kinase; GSK3B: Glycogen synthase kinase 3 beta; PKC: Protein kinase C; NF-κB: Nuclear factor-κB; MDM2: Mouse double minute 2 homolog; DISC: Death-inducing signaling complex; FADD: Fas-associated protein with death domain; IAP: Inhibitor of apoptosis; Bcl-2: B-cell lymphoma 2; Bax: Bcl-2-associated X protein; Bad: Bcl-2-associated agonist of cell death; SVV: Survivin; Cyto. C: Cytochrome c; SMAC: Second mitochondria-derived activator of caspases; CDK: Cyclin-dependent kinase.

the optimum dose in the body. Nanotechnology brings multiple advantages to the targeted delivery of natural products in the treatment of cancers. The utilization of nanoparticles along with natural components can increase the bioavailability, targeting, and controlled-release profiles of these agents (10). One of the first studies that employed nanoparticles in the field of delivery of leukemia and lymphoma drugs was done in the 1990s (117, 118). Preliminary studies were concerned with pharmacokinetic behavior and plasma concentration of a vincristine sulfate liposome system. that was FDA-approved under the name Marqibo® as an injected nano-drug used against relapsed Ph-ALL (Philadelphia chromosome-negative ALL) in adults (119). Recently, the safety profile and clinical benefit of Marqibo® was assessed for the adolescent young adult population and for children, and it was reported to exhibit safety and efficiency profiles similar to those obtained for adult patients (120, 121). Another study that demonstrated the applicability of nanoparticles for ALL was done by Changhui Liu et al (122). The targeted nano-containers were able to deliver and

Table 3. Plant-derived natural products used in combination with other cytotoxic agents in clinical trials for leukemia and lymphoma.

Plant	Drug	Other name	Mechanism of action	In combination with	Hematologic Neoplasia	Clinical trial
Taxus brevifolia	Paclitaxel	Taxol	Microtubule Inhibition	Carboxyamidotriazole	Refractory lymphomas	Phase II
				Topotecan and Filgrastim-SD/01	Relapsed and refractory aggressive NHL	Phase II
				Avelumab, bevacizumab, capecitabine, cyclophosphamide, 5-Fluorouracil (5-FU), leucovorin, nab-paclitaxel, Lovaza, Oxaliplatin, Rituximab, ALT-803, ETBX-061 and haNK	Relapsed CD20-positive NHL	Phase II
				Monoclonal antibody therapy and Cyclosporine	Recurrent or refractory NHL	Phase I
				Estramustine	Relapsed or refractory NHL	Phase I
				L-778,123	Recurrent or refractory lymphomas	Phase I
				Ifosfamide and Teniposide	Relapsed NHL	Phase II
				Cyclophosphamide and Dexamethasone	Relapsed or refractory MM	Phase II
				Lenalidomide (Revlimid)	Relapsed/refractory MM	Phase II
Amoora rohituka	Alvocidib	Flavopiridol, DSP-2033	CDK9 inhibition	Venetoclax	AML	Phase I
				Cytarabine/Daunorubicin	AML	Phase I
				Cytarabine, and Mitoxantrone Hydrochloride or Cytarabine and Daunorubicin Hydrochloride	AML	Phase II
				Cytarabine and Mitoxantrone	Newly diagnosed acute leukemia	Phase II
				Cytarabine, and Mitoxantrone	Acute Leukemia	Phase II
				Vorinostat	Relapsed/refractory acute leukemia or CML	Phase I
				Fludarabine Phosphate, and Rituximab	LPDs or MCL	Phase I
Maytenus serrata	Maytansine	Maitansine	Microtubule assembly inhibition	SAR3419	Leukemia	Phase II
				Lorvotuzumab Mertansine (IMGN901)	ALL	Phase II
				LOP628	AML	Phase I
Pomegranate	Ellagic acid	Benzoaric acid	Anti-proliferative, apoptotic, antioxidant	Dietary intervention:¬¬ Omega 3 fatty acid, L-Selenomethionine, Allicin, resveratrol, quercetin, Epigallocathechin gallate	Follicular lymphoma	Phase II
Salvia miltiorrhiza	Tanshinone I	TTE-50	Anti-proliferative and apoptotic	ATO, RIF, ATRA, mitoxantrone, Ara-C, MTX and 6MP	APL	Phase IV

Abbreviations: NHL, Non-hodgkin lymphoma; **MM,** Multiple myeloma; **AML,** Acute myeloid leukemia; **LPDs,** Lymphoproliferative disorders; **CML,** Chronic myeloid leukemia; **MCL,** Mantle cell lymphoma; **ALL,** Acute lymphoblastic leukemia; **APL,** Acute promyelocytic leukemia.

selectively release the entrapped paclitaxel drug into ALL cells (CEM and Ramos). Not only this drug delivery system targets ALL cells and leaves normal cells but also decreases the occurrence of some side effects of paclitaxel, leading toward better therapeutic efficacy in CEM-tumor-bearing mice (123). In addition, solid-lipid (one type of nanoparticle) formulation of a natural chemotherapeutic agent, AP9-cd, which was isolated from a dry waste wood powder of Cedrus deodara, was recently reported (124). This formulation showed improved anti-leukemic effect both in vitro and in vivo in comparison with conventional drug systems in drug efficacy, pharmacokinetics, and biodistribution aspects (123).

Although there are many advantages to apply nanotechnology for better delivery of natural components, it is not without challenges. Nanoparticles' potential toxicity is a major concern, partly because they can cross biologi¬cal membranes, such as cellular membranes (126, 127). Another challenge that arises when using nanoparticles as drug delivery agents is that the nanoparticle will undergo changes in the body. This must be taken into account because these changes could affect the bioavail¬ability, targeting, and release kinetics of the drug (10). Nonetheless, many researchers believe that nanomedicines will shift the paradigm of cancer treatment and that the true goal of cancer nano¬medicine will become a reality in the foreseeable future.

4.2. Antibody-drug conjugates (ADCs)

A burgeoning class of monoclonal antibody therapies, called antibody-drug conjugates (ADCs), delivers dual therapies in a single cancer cell-killing package (128). The localized delivery and release of the cytotoxic agent attached to a monoclonal antibody within or near malignant cells allow for the targeted delivery of a potent cytotoxic agent to antigen-positive cancer cells while reducing damage to antigen-negative normal cells (129). Mylotarg (gemtuzumab ozogamicin; GO) is a conjugate of a humanized monoclonal antibody that targets the CD33 antigen on leukemia cells with

a prodrug form of calicheamicin, a natural product derived from the bacterium Micromonospora echinospora (a species of bacteria) (130, 131). GO was the first antibody-drug conjugate approved for the treatment of AML by the FDA via the accelerated approval process in 2000 (132,133). Once bound to the leukemia cells, the conjugate is internalized and then breaks down, allowing calicheamicin to target a specific region of the minor groove of DNA (134). Two other immunoconjugates brentuximab vedotin (Adcetris®) (135) and trastuzumab emtansine (Kadcyla®) (136) were marketed in 2011 and 2013, respectively. Adcetris® targets the protein CD30, which is expressed in systemic anaplastic large cell lymphoma and classical Hodgkin lymphoma. This antibody is conjugated to a fully synthetic analogue of the antimitotic agent dolastatin, a linear pentapeptide originally isolated from the extracts of the sea hare Dolabella auriculari (a species of sea slug) (137).

Despite the importance of antibody-conjugated natural products derived from different sources (bacteria, sea slug, etc.) in the treatment of hematological malignancies, there has been no approved conjugated drug that derived from plant sources. Nevertheless, the promising news in this era is that many studies are now investigating conjugated plant-derived natural products in pre-clinical levels. For example, a study was designed to determine whether antibodies against human chorionic gonadotropin beta (hCG) conjugated to curcumin can selectively kill leukemic cells expressing hCG. This study was carried out on MOLT-4 and U-937 cells expressing hCG and on peripheral blood leukocytes of AML patients. The resulting data showed that antibody against hCG linked to curcumin has potential for therapy of hCG-expressing leukemia (138). Taken together, application of ADC strategy is a renewed interest in plant-derived natural products that are highly cytotoxic agents but suffer from lack of good drug-like properties and narrow safety margins when systemically administered as common chemotherapeutic drugs.

5. Conclusion

Since there are some important challenges related to using conventional therapeutic drugs for patients with leukemia and lymphoma, it is considered so necessary to find new agents that would be more efficient. Medicinal plants have historically been a rich source for successful anti-leukemic drugs, and still represent a rich pool for the identification of new pharmacological leads. We are accepting that nature has already carried out the combinatorial chemistry; all we have to do is sometimes refine the structures. In addition, since the efficient in vivo uptake of leukemic cells requires better targeting moieties to improve cellular uptake and reduced toxicity to contiguous normal cells, many researchers are now investigating to find more targeted agents. Targeted therapy in leukemia and lymphoma treatment has made immense progress towards generating molecules that show great clinical benefit, resulting in FDA approval of some drugs such as Marqibo and the clinical development of many more. Clearly, there is ample scope for new discoveries to be made of natural products from plants with promising activities against leukemia and lymphoma. Finally, since most of today's natural products in clinical use were discovered through a routine examination of plants, so serendipity is still an important route of discovery.

Conflict of interest

The authors declare no conflict of interest.

Research involving human participants and/or animals

This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent

For this type of study, informed consent is not required.

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