Natural Compounds and Lymphoma

Subjects: Oncology

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Lymphoma is a group of blood malignancies that develop from lymphocytes

A natural product is a chemical compound or substance produced by a living organism—that is, found in nature. In the broadest sense, natural products include any substance produced by life.

Cancer systems biology encompasses the application of systems biology approaches to cancer research, in order to study the disease as a complex adaptive system with emerging properties at multiple biological scales.

lymphoma | cancer system biology | natural products | apoptosis | cell cycle arrest

1. Microorganism-Derived Compounds and Lymphoma

Microorganisms with a microscopic size are referred to as prokaryotes. Fungi, which are classified as eukaryotes, are also included in microorganisms in a broad sense. In recent decades, it has been reported that microorganism-derived compounds have various bioactivities including antioxidant and antitumor effects [1][2] (Table 1). According to studies, microorganism derived compounds induced cell cycle arrest at the G2/M phase and inhibited tubulin assembly; subsequently, it triggered apoptosis in colon cancer cells [3]. Several natural compounds from *Aspergillus fumigatus* YK-7 significantly inhibited growth of U937 cells after three days of treatment; the natural compounds included pyripyropene E, alismol, helvolic acid, and β-5, 8, 11-trihydroxybergamot-9-ene [4]. These toxic effects against lymphoma cell lines supported the potential of natural compounds as active agents to treat various types of lymphoma. Bao et al. isolated new compounds from the coculture of marine-derived fungi *Aspergillus sclerotiorum* and *Penicillium citrinum* [5]. Among the compounds, aluminiumneohydroxyaspergillin exhibited cytotoxicity against the U937 cell line (IC50 = 4.2 μM). L. Hammerschmidt et al. isolated twelve compounds from *Gymnascella dankaliensis* ethyl acetate extract and measured their cytotoxicity against the L5178Y cell line [6]. Four compounds were found to have cytotoxicity. Aranorosin-2-methylether, aranorosin, and gymnastatin A showed potent cytotoxic activity against L5178Y cells with IC50 values of 0.44, 0.58, and 0.64 μM, respectively. Gymnastatin B had moderate cytotoxic activity with an IC50 value of 5.8 μM. Three natural products isolated from *Aspergillus carneus,* isopropylchetominine, sterigmatocystin, and astelotoxin E showed significant cytotoxicity against mouse lymphoma cell L5178Y (IC50 0.04, 0.3, and 0.2 μM, respectively) [7]. Bromophilone B isolated from sponge-associated fungus *Penicillun canescens* displayed cytotoxicity against L5178Y, a mouse lymphoma cell line (IC50 8.9 μM) [8]. *Penicillium citrinum* var. originated natural compounds, including 5-methyl alternariol ether, methyl, 8-hydroxy-6-methyl-9-oxo-9H-xanthene-1-carboxylate, and citriquinochroman, showed toxic events against L5178Y cells each at doses of IC50 0.78, 1.0 μg/mL, IC50 0.78, 1.0 μg/ml, and IC50 6.1 μM [9] [10]. Cladosporinone and viriditoxin which are derived from *Cladosporium Cladosporioides* (Fresen). G.A. de Vries also induced cytotoxicity when administered to L5178Y cells in IC50 0.88 and 0.1 μM [11]. Verticillin D and new

cyclic heptapeptides Cyclo-(Gly-D-Leu-D-allo-Ile-L-Val-L-Val-D-Trp-β-Ala) isolated from soil-derived fungus *Clonostachys rosea* displayed significant cytotoxicity against L5178Y mouse lymphoma cell lines (IC50 0.1 and 4.1 μM, respectively) [12]. Yu et al. investigated metabolites from ascomycete fungus *Aphanoascus fulvescens* isolated from goose dung [13]. Indole alkaloids, okaramine A, C, G, and H were evaluated to induce cytotoxicity against L5178Y cell lines at different IC50 concentrations, among which okaramine G showed the highest significance. Umeokoli et al. isolated 9 compounds from *Lasiodiplodia theobromae* M4.2–2 [14]. Among the compounds, 1 H-Dibenzo (b,e) (1,4) dioxepin-11-one, 3, 8-dihydroxy-4-(methoxymethyl)-1, 6-dimethyl exhibited potent cytotoxicity against L5178Y mouse lymphoma cell lines (IC50 = 7.3 μM). P.F. Uzor et al. isolated three compounds from the fungus *Nigrospora oryzae* and six compounds from its host plant, *Combretum dolichopetalum* [15]. Two out of these nine compounds were found cytotoxic against L5178Y cells through the cytotoxicity assay (MTT). 4-dehydroxyaltersolanol A from *Nigrospora oryzae* ethyl acetate extract had the IC50 value 9.4 μM, and 3, 3′, 4-tri-O-methylellagic acid from *Combretum dolichopetalum* methanol extract showed the IC50 value of 29.0 μM. 9-Ethyliminomethyl-12-(morpholin-4-ylmethoxy)-5,8,13,16-tetraaza -hexacene-2,3-dicarboxylic acid (EMTAHDCA) isolated from fresh water cyanobacterium *Nostoc* sp. MGL001 showed significant cytotoxicity against the DLA cell, concomitant with 372.4 ng/mL of IC50 value [16]. As shown in Table 1, twenty-seven compounds from microorganism exert cytotoxicity against lymphoma cell lines. Among them, Alismol, Helvoic acid, and β-5,8,11-trihydroxybergemot-9-ene from *Aspergillus fumigatus* YK-7 had IC50 values more than 50 μM, but several compounds, including aranorosin and gymnastatin A from *Gymnascella dankaliensis,* were less than 1 μM [4]. These are somewhat prominent values compared with other values.

Table 1. Microorganism-derived compounds and lymphoma.

Compound	Source	Cell Line/Animal Model	Dose; Duration	Efficacy	Reference
Alismol	*Aspergillus fumigatus* YK-7	U937	IC50 67.1 μM; 3 days	Inhibition of proliferation	[4]
aluminiumneohydroxyaspergillin	Co-culture of *Aspergillus sclerotiorum and Penicillium*	U937	IC50 4.2 μM; 48 h	Induction of cytotoxicity	[5]
Aranorosin	*Gymnascella dankaliensis*	L5178Y	IC50 0.58 μM	Induction of cytotoxicity	[6]
Aranorosin-2-methylether	*Gymnascella dankaliensis*	L5178Y	IC50 0.44 μM	Induction of cytotoxicity	[6]
Asteltoxin E	*Aspergillus carneus*	L5178Y	IC50 0.2 μM	Induction of cytotoxicity	[7]

Compound	Source	Cell Line/Animal Model	Dose; Duration	Efficacy	Reference
Bromophilone B	*Penicillium canescens*	L5178Y	IC50 8.9 μM	Induction of cytotoxicity	[8]
Citriquinochroman	*Penicillium citrinum,* var	L5178Y	IC50 6.1 μM	Induction of cytotoxicity	[10]
Cladosporinone	*Cladosporium Cladosporioides (Fresen.)* G.A. de Vries	L5187Y	IC50 0.88 μM	Induction of cytotoxicity	[11]
Cyclo-(Gly-D-Leu-D-allo-Ile-L-Val-L-Val-D-Trp-β-Ala)	*Clonostachys rosea*	L5178Y	IC50 4.1 μM	Induction of cytotoxicity	[12]
Gymnastatin A	*Gymnascella dankaliensis*	L5178Y	IC50 0.64 μM	Induction of cytotoxicity	[7]
Gymnastatin B			IC50 5.80 μM		[6]
Helvolic acid	*Aspergillus fumigatus* YK-7	U937	IC50 57.5 μM; 3 days	Inhibition of proliferation	[4]
Isopropylchetominine	*Aspergillus carneus*	L5178Y	IC50 0.4 μM	Induction of cytotoxicity	[7]
methyl 8-hydroxy-6-methyl-9-oxo-9H-xanthene-1-carboxylate	*Penicillium citrinum* var.	L5178Y	IC50 0.78, 1.0 μg/mL	Induction of cytotoxicity	[9]
Okaramine A	*Aphanoascus fulvescens (Cooke)* Apinis	L5178Y	IC50 4.0 μM	Induction of cytotoxicity	[13]
Okaramine C			IC50 12.8 μM		
Okaramine G			IC50 13.8 μM		
Okaramine H			IC50 14.7 μM		

Compound	Source	Cell Line/Animal Model	Dose; Duration	Efficacy	Reference
Pyripyropene E	*Aspergillus fumigatus* YK-7	U937	IC50 4.2 μM; 3 days	Inhibition of proliferation	[4]
Sterigmatocystin	*Aspergillus carneus*	L5178Y	IC50 0.3 μM	Induction of cytotoxicity	[7]
Verticillin D	*Clonostachys rosea*	L5178Y	IC50 0.1 μM	Induction of cytotoxicity	[12]
Viriditoxin	*Cladosporium*	L5187Y	IC50 0.1 μM	Inhibition of proliferation	[11]
1H-Dibenzo (b, e) (1, 4) dioxepin- 11- one,3, 8-dihydroxy- 4-(methoxymethyl)-1,6-dimethyl	*Lasiodiplodia theobromae*	L5178Y	IC50 7.3 μM	Induction of cytotoxicity	[14]
4-Dehydroxy-altersolanol A	*Nigrospora oryzae*	L5178Y	IC50 9.4 μM	Induction of cytotoxicity	[15]
5-methyl alternariol ether	*Penicillium citrinum* var.	L5178Y	IC50 0.78, 1.0 μg/mL	Induction of cytotoxicity	[9]
9-Ethyliminomethyl-12-(morpholin-4-ylmethoxy)-5,8,13,16-tetraaza -hexacene-2,3-dicarboxylic acid	cyanobacterium *Nostoc* sp.	DLA	IC50 372.4 ng/mL; 24 h	Induction of cytotoxicity	[16]
β-5,8,11-trihydroxybergamot-9-ene	[17] *Aspergillus fumigatus* YK-7	U937	IC50 84.9 μM; 3 days	Inhibition of proliferation	[4]

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arctigenin-a natural compound which has been studied for various bioactivity [18]. Arctigenin increased c-caspase-3, -9, and cleaved poly ADP ribose polymerase (c-PARP) in BC3, and triggered dissipation of mitochondrial membrane potential (MMP) together with decreased ATP production in BC3 and Ramos. Additionally, arctigenin induced up-regulation of transcriptional expressions of CHOP and ER stress-induced ER chaperon glucose-related protein (GRP) 94, while down-regulating GRP78 and activating transcription factor 6α (ATF6α) in PEL cells. Furthermore, arctigenin reduced the levels of p-p38 and p-extracellular signal-regulated kinase (ERK) 1/2, which play an important role in survival and apoptosis. Zhao et al. reported that the treatment of curcumin induced the antitumor effect on CH12F3 cell lines through DNA break and apoptosis [19]. This compound increased expression of nuclear γH2AX, PAPR1, and proliferating cell nuclear antigen (PCNA), while decreasing Rad51 involved in homologous recombination which is essential for DNA repair. Additionally, up-regulation of caspase-3 and -9 was observed. These results showed that caspase-dependent apoptosis as well as DNA damage and impaired Rad51-dependent homologous recombination could be induced by curcumin. Tafuku et al. reported that natural carotenoid

9-Ethyliminomethyl-12-(morpholin-4-ylmethoxy)-5, 8, 13, 16-tetraaza -hexacene-2, 3-dicarboxylic acid (EMTAHDCA).

fucoxanthin (FX) and fucoxanthinol (FXOH) extracted from the brown seaweed *Cladosiphon okamuranus* Tokida showed an antitumor effect on BL and HL in vitro [20]. In many lymphoma cells, these compounds induced apoptosis (Raji, Daudi, B95-8/Ramos cell) and halted proliferation (Daudi, KM-H2, L540 cell) through cell cycle arrest at the G1 phase. In addition to the increase in c-PARP, c-caspase-3, and -9, the decrease in antiapoptotic and cell cycle regulatory proteins, including Bcl-2, cIAP-2, X-linked inhibitor of apoptosis protein (XIAP), cyclin D1, cyclin D2, was observed in Daudi after FXOH treatment. Additionally, the inhibition of nuclear factor κB (NFκB)-DNA binding activity was observed in Daudi by using electrophoretic mobility shift assay. These results indicated that FXOH induced apoptosis by decreasing NFκB-DNA binding activity, followed by inhibition of antiapoptotic and cell cycle regulatory proteins. Mottaghipisheh et al. confirmed that various compounds isolated from *Ducrosia anethifolia* inhibited proliferation in L5178Y parent (PAR) and multidrug resistance (MDR) cells [21]. Among compounds, pabulenol, (þ)-oxypeucedanin hydrate, oxypeucedanin, oxipeudanin methanolated, imperatorin, isogospherol, heraclenin, and heraclenol had IC50 values for antiproliferation against L5178Y MDR cells, as well as L5178Y PAR cells. All values were indicated in the table and were less than 60.58 μM. Nakano et al. proposed the antiproliferative effects of MeOH extracts of aerial parts of *Citrus tachibana* against MT-1 and MT-2 cells [22]. Six phenanthroindolizidine alkaloids isolated from this extract showed antiproliferative activities at different EC50 values. Among the compounds, 3-demethyl-14a-hydroxyisotylocrebrine N-oxide showed toxicity in normal cells, while 3-demethyl-14b-hydroxyisotylocrebrine showed better potency than doxorubicin—a drug that is clinically used for antineoplasm. Methyl angolensate is a tetranortriterpenoid extracted from the root callus of *Soymida febrifuga,* called an Indian red wood tree [23]. Amounts of 10, 50 ,100, 250 μM of methyl angolensate solution treatment for 24, 48, 72 h to Daudi cells caused the inhibition of cell proliferation, induction of apoptosis, ROS formation, and loss of mitochondrial transmembrane potential. These results suggest that methyl angolensate induces apoptosis through the mitochondrial pathway, supported by the induction of PARP cleavage. Further research revealed that methyl angolensate treatment facilitates DNA double-strand break repair by upregulation of nonhomologous DNA end joining (NHEJ) proteins including KU70 and KU80. These findings are in line with the upregulation of MRE11, RAD50, NBS1, and pATM, and downregulation of p53 and p73. Peperobtusin A extracted from *Peperomia tetraphylla* induced cell cycle arrest at the S phase and then apoptosis in U937 [24]. As for mechanisms, peperobtusin A decreased MMP, Bid, caspase-3, and p38 while increasing ROS, c-caspase-8, -9, -3, and p-p38. Dissipation of MMP and ROS accumulation has been known to be involved in mitochondrial dependent apoptosis and cell death, respectively. Additionally, expression of Bcl-2, an antiapoptotic protein, was reduced, and Bax, a proapoptotic protein, was increased after peperobtusin A treatment. Taken together, the antitumor effect of peperobtusin A on U937 was induced by regulating the levels of pro-, antiapoptotic proteins, ROS, and MMP. Psilostachyin C, derived from *Ambrosia* spp. is among the types of sesquiterpene lactones [25]. Martino et al. reported that this natural compound (10 μg/ml for 24 h) showed significantly induced early and late apoptosis, necrosis, and cell cycle arrest at the S phase in murine lymphoma cell lines BW5147. Decreased levels of antioxidant enzymes such as superoxide (SOD), catalase (CAT), and peroxidase (Px) and up-regulation of rhodamine 123 negative cells were also reported. These results confirmed the efficacy of psilostachyin C to interfere with proliferation as well as mitochondrial functioning of lymphoma cells. Jara et al. reported that resveratrol exerted antiproliferative and proapoptotic effects on BL cell line Ramos [26]. Protein levels of apoptotic marker c-caspase-3 and c-PARP were increased. mRNA levels of proapoptotic mediators Noxa and p53

upregulated modulator of apoptosis (PUMA) also increased. In addition, resveratrol induced the up-regulation of primary double strand break sensor proteins as well as DNA damage and repair-related proteins including Rad50, Mre11, p-p95, p-ATM, p-BRCA1, γ-H2AX, DNA-PKcs, and KU80. These data suggested that resveratrol could regulate expression of genes with respect to DNA response, and then exert antiproliferative and apoptotic effects. Sui et al. adduced evidence that resveratrol regulates cell cycle arrest and apoptosis in extra nodal NK/T cell lymphoma (NKTCL) cell lines such as SNT-8, SNK-10, and SNT-16 [27]. After treatments, inconsistency for the percentage of cell cycle phase compared with untreated NKTCL cell lines was observed. Resveratrol induced an increase in the S phase with down-regulated expression of cyclin A2 which plays an important role in cell cycle progression. Decreased expression of Mcl-1 and survivin, and increased expression of Bax, Bad, c-caspase-3 and -9 were also observed. Phosphorylation of AKT and Stat3, known to be involved in proliferation, was inhibited by resveratrol. Furthermore, DNA damage response related proteins, including p-ATM, γ-H2A.X., p-chekpoint kinase (Chk) 2, and p-p53, were affected, and then increased. Schweinfurthins are natural compounds originated from *Macaranga alnifolia* Baker and are classified as members of the stilbene group [28]. Treatment of schweinfurthins at a dose of 100 nM against WSU-DLCL2, a phosphatase and tensin homolog (PTEN) deficient B cell lymphoma cells for 24 h increased the phosphorylation of eukaryotic initiation factor 2a (p-EIF2a) while decreasing the level of mTOR-AKT. Especially, schweinfurthin G elicited strong antiproliferative activities against three types of PTEN deficient B cell lymphoma cells—RL, SU-CHL-10, and WSU-DLCL2. These findings identified the potent inhibitory activities of this natural compound to treat PTEN deficient B cell lymphoma cells. Thymoquinone is a subtype of benzoquinone which was isolated from *Nigella sativa* Linn. Hussain et al. reported that thymoquinone (5 and 10 mM for 24 h) induced apoptosis and released ROS in activated B cell lymphoma cell lines (ABC-DLBCL) [29]. Nuclear compartments of HBL-1 and RIVA cell lines showed decreased translocation and phosphorylation of p65. Activation and cleavage of caspase-9, caspase-3, PARP, and Bax were examined, and inhibition of IκBa, XIAP, and survivin was also reported. It was also confirmed that thymoquinone treatment downregulated NFκB, and its transcriptional targets, Bcl-2 and Bcl-xL, subsequently decreased. Additionally, it was found that combination treatment of thymoquinone and TRAIL sufficiently inhibited cell viability and apoptosis, while each drug showed no effect when treated alone. These findings demonstrated that thymoquinone induced caspase and mitochondria dependent apoptosis against ABC-DLBCL. Hussain et al. administered thymoquinone to four primary effusion lymphoma cell lines—BC-1, BC-3, BCBL-1, and HBL-6, at the dose of 10 and 25 μM for 24 h [30]. Phosphorylation of AKT, forkhead box protein O1 (FOXO1), glycogen synthase kinase (GSK) 3, and Bad were suppressed in BC-1, BC-3, and BCBL-1 cells, suggesting that apoptosis was induced via the mitochondrial pathway. ROS release detected in BC-1 cells resulted in Bax activation and Bcl-2 inhibition. BC-1 and BC-3 cells showed cleavage of caspase-9, caspase-3, and PARP. Death receptor (DR) 5 upregulation was observed in BC-1 and BC-3 cells, but did not seem to be involved in thymoquinone-induced apoptosis. An alkaloid 4-Deoxyraputindole C extracted from *Raputia praetermissa* induced cell death in Raji—a lymphoma cell line [31]. As for cell death, this compound decreased cell membrane integrity and increased lysosomal permeabilization. Additionally, dissipation of MMP and production of mitochondrial superoxide were observed by this compound. Cathepsins B/L, known as apoptosis and necrosis relating factors, were shown to be suppressed (IC 50 28.4 ± 1.2 μM and 1.7 ± 0.1 μM, respectively). Namely, 4-Deoxyraputindole C not only attenuates membrane integrity, MMP, and cathepsin but also increases the mitochondrial superoxide level. β-Asarone, known to show bioactivity such as

anti-inflammation, revealed that it also induced antiproliferation and apoptosis in the lymphoma cell line Raji [32]. As a result of flow cytometry, an increase in the percentage of apoptotic cells after β-Asarone treatment was observed. The expression of c-caspase-3, -9, and c-PARP involved in intrinsic apoptosis was also up-regulated. Furthermore, decreased nuclear expression and phosphorylation of NFκB were confirmed, and TNFα-associated nuclear translocation of NFκB was reduced by treatment. Chen et al. demonstrated the mechanism of the anticancer activity of β-phenethyl isothiocyanate (PEITC) [33]. Administered to Raji cells, 10 μM PEITC increased cellular H_2O_2 levels and rapidly depleted cellular and mitochondrial glutathione. This led to the attenuation of mitochondrial respiration rate, following the disruption of mitochondrial respiratory complex I. NDUFS3, a mitochondrial respiratory complex I subunit, was especially the target of such disruption. Paterna et al. elucidated that dregamine and teberanaemontanine derivatives, which are indole alkaloids isolated from *Tabernaemontana elegans* Stapf. showed regulating effects against the proliferation of L5178Y cells [34]. Compounds 6, 8, 9, 10, 15, 16, and 23 induced cytotoxicity in significant IC50 levels, being ineffective in noncancerous mouse embryonic fibroblast NIH/3T3 cell line. Moreover, compounds 8, 9, 10, and 15 displayed strong MDR reversal activity, suggesting the potentiality of these derivatives to regulate lymphoma cell lines.

2.2. In Vitro and In Vivo Studies

Kumar et al. reported that chelerythrine, which originated from *Chelidonium majus*. L., is a rising antitumor agent given the previous reports proving its effects as a selective inhibitor of protein kinase C [35]. It was observed that survival duration was increased, and growth of Dalton's Lymphoma cells were reduced in BALB/c (H2d) mice when treated with this compound at 1.25 or 2.5 mg/kg for 34 days. It was also investigated that this compound (2.5 mg/kg) upregulated activating receptor NKG2D while downregulating inhibitory receptor NKG2A in TANK cells. These results supported the profound pharmaceutical activity of chelerythrine as a replacement for conventional therapies to treat lymphoma. Peters et al. demonstrated that elatol, a marine-derived natural compound, has effects of antiproliferation and apoptosis on lymphoma cell lines through translational inhibition of oncoproteins such as MYC, BCL-2, etc. [36]. It was confirmed that decreased proliferation and increased apoptosis were observed in SU-DHL-6, OCI-Ly3, and RIVA cells by elatol treatment. Of the cell lines, SU-DHL-6 and OCI-Ly3 were subject to further experiments. Results showed decrease in proteins expression, including cyclinD3, MYC, MCL1, PIM2, BCL2, and survivin, which were related in proliferation and apoptosis. Additionally, eIF4A activity which involved in translation was decreased by elatol. Furthermore, as results of in vivo experiment using xenograft mice, a reduction in tumor volume after elatol treatment for several weeks was observed. Yamamoto et al. reported that FX and FXOH induced apoptosis and cell cycle arrest in primary effusion lymphoma cells [37]. After treatments, increased levels of c-PARP, c-caspase-3, -8, and -9 were observed in BCBL-1 and TY-1. Following all experiments conducted on BCBL-1, decreased levels of antiapoptotic proteins Bcl-xL and XIAP were detected by both compounds. In addition, FXOH reduced survivin expression, AP-1 binding, and NFκB-DNA binding activity. pRb, known as cell cycle regulator, phosphorylation, and cell cycle regulatory proteins, including cyclin D2, cyclin dependent kinase (CDK) 4/6, and c-Myc, were decreased by treating both FX and FXOH. After treatments, the levels of p-IκB kinase (IKK) β, p-IκB α, IKK α, IKK β, IKK γ, Akt, phosphoinositide dependent protein kinase (PDK) 1, JunB, JunD, p-caspase-9, and β-catenin were also decreased. Moreover, FX treatment caused the loss of tumor weight in mice compared to untreated. These findings supported the potential of FX and FXOH for PEL therapeutic

use. Yu et al. reported that cell cycle arrest at the G0/G1 phase and apoptosis were induced by pterostilbene (PTE) in mantle cell lymphoma cell lines [38]. In mantle cell lymphoma cell lines Jeko-1, Granta-519, Mino, and Z-138, significant cytotoxicity was revealed, and percentage of apoptotic cells was also increased by PTE treatment. Further experiments were executed with Jeko-1 and Granta-519. While increasing expression of c-caspase-3, -8, -9, and Bax, PTE decreased expression of Bcl-2 and Bcl-xL. Additionally, PTE treatment induced dissipation of MMP and reduced expression of CDK4, CDK6, and cyclinD1, which are related in the cell cycle. Furthermore, a decrease in p-PI3K, p-Akt, p-mTOR, and p-p70S6K, which are involved in inactivation of the signaling pathway was observed. In the JeKo-1 xenograft model, expression of p-mTOR was decreased, and tumor growth was inhibited by PTE compared to the control treatment. Singh et al. studied the efficacy of resveratrol, a polyphenolic phytoalexin compound derived from various plants, including red grapes, mulberries, peanuts, and Japanese knotweed [39]. In this study, NOD/SCID mice were subcutaneously injected with EL4 cells. Five days post injection, they were orally treated with vehicle or resveratrol (10, 50, and 100 mg/kg) every day. Resveratrol suppressed EL4 tumor growth and increased survival time in a dose dependent manner. A following in vitro approach revealed that resveratrol (5, 10, 25, 50, 100 μM for 6, 12, 24 h) induced apoptosis of EL4 cells by elevating the expressions of AhR, Fas, FasL, Bax, Bid, cytochrome-c, sirtuin (SIRT) 1, cleaved caspase-8, -3, -9, and cleaved PARP and suppressing the phosphorylation of IκBα and expression of NF-κB. Xiao et al. verified that 11(13)-dehydroivaxillin (DHI) has antitumor effects on NHL cell lines, including Daudi, NAMALWA, SU-DHL-2, and SU-DHL-4, as well as xenograft mice [40]. To confirm the change in the percentage of apoptotic cells, flow cytometry analysis was used, and increased apoptosis was observed by DHI treatment in NHL cell lines. Cleavage of casapse-3 and PARP was shown in SU-DHL-2 and NAMLWA except Daudi and SU-DHL-4. The mRNA levels of IκB, cyclinD1, and Bcl-2 were decreased in Daudi, NAMALWA, and SU-DHL-2. The protein levels of p-IκBα, p-p65, IKKα/β, c-MYC, cyclinD1, and NF-κB were also reduced in Daudi and SU-DHL-2. Moreover, it was observed that DHI treatment induced the loss of tumor weight in experiments using an NHL xenograft mice model. As a result of immunohistochemistry (IHC), decreased proliferation markers, including PCNA, IKKα, and IKKβ were also confirmed. A number of plant-derived compounds were reported to have an effect on lymphoma cell lines, and they were studied focusing on cell cycle arrest, DNA repair, and the apoptosis pathway like other cancers. There were two studies on the effect of FXand FXOH extracted from *Cladosiphon okamuranus* Tokida on lymphoma cell line [20][37]. Both compounds showed cytotoxicity against lymphoma cell lines, including Daudi and BCBL-1, and upregulation of c-caspase-3, -8, -9, and c-PARP, which stand for apoptosis, was observed. Interestingly, studies taking both compounds reported that expressions of antiapoptotic proteins such as XIAP and Bcl-2 as well as NF-κB activity were reduced. It was also observed to induce cell cycle arrest at the G1 phase with decreased expression of the cell cycle regulator. In addition to in vivo study, an in vitro study using BCBL-1 xenograft model confirmed tumor weight loss after treatment with FXOH. These results could contribute to the development of an advanced drug for lymphoma. Psilostachyin C induced cell cycle arrest at the S phase, apoptosis, and necrosis in BW5147 cell lines [25]. A decrease in antioxidant enzymes and an increase in rhodamine 123 negative cells were also observed. Thus, research describes that this compound has both effects of antiproliferation and interfering mitochondrial function in lymphoma cell lines. As for ROS, methyl angolensate from *Soymida febrifuga* induced ROS generation, MMP dissociation, and apoptosis in Daudi cell lines. Additionally, proteins associated with NHEJ, a DNA repair mechanism, such as KU70 and KU80 were increased by this compound. Thymoquinone isolated from *Nigella*

sativa was also observed by two studies. One reported the effect of this compound on activated BL and the other on PEL [29][30]. Both studies dealing with different types of lymphoma demonstrated that ROS generation was induced, followed by mitochondria mediated apoptosis by thymoquinone. Well known phytochemical resveratrol was also used in three different studies [26][27][39]. Resveratrol induced apoptosis of BL, NKTCL, murine lymphoma cell lines. Primary double strand sensor proteins and DNA damage and repair proteins, including Rad50, Mre11, p-ATM, p-BRACA1, DNA-PKcs, and KU80 were increased in BL cell lines by resveratrol. In NKTCL cell lines, DNA damage response related proteins, including p-ATM, γ-H2A.X., p-Chk2, and p-p53 were also affected by resveratrol. In addition to in vitro, it was observed that resveratrol suppressed EL4 tumor growth.

Table 2. Plant-derived compounds and lymphoma.

System	Compound	Source	Cell Line/Animal Model	Dose; Duration	Efficacy	Mechanism	Reference
In vitro	Amorphispirononeses B	*Amorpha fruticosa*	L5178Y	IC50 7.6 μM	Induction of cytotoxicity		[17]
In vitro	Arctigenin		BC3	Glucose(-), 5 μM; 2, 4, 6 h	Induction of apoptosis	↑ c-caspase-3, -9, c-PARP	[18]
			BC3, Ramos	Glucose(-), 1, 5, 10 μM		↓ MMP, ATP	
			BC3, BCBL1	Glucose(-), 5, 10 μM; 3, 4, 6 h		↑ GRP94, CHOP ↓ p-p38, p-ERK1/2, p-p90RSK, GRP78, ATF6α	
			Ramos, DG75	Glucose(-), 5 μM, 4, 6 h		↑ GRP94, CHOP ↓ GRP78, ATF6α	
In vitro	Curcumin		CH12F3	3, 6, 9, 10, 20, 30, 40, 50 μM; 4, 24 h	Induction of DNA damage and apoptosis	↑ γH2AX, PAPR1, PCNA, caspase-3, -9 ↓ Rad51	[19]
In vitro	Dalbinol	*Amorpha fruticosa*	L5178Y	IC50 0.2 μM	Induction of cytotoxicity		[17]

System	Compound	Source	Cell Line/Animal Model	Dose; Duration	Efficacy	Mechanism	Reference
	Dalpanol	*Amorpha fruticosa*	L5178Y	IC50 0.7 μM	Induction of cytotoxicity		[17]
	Deguelin	*Amorpha fruticosa*	L5178Y	IC50 0.2 μM	Induction of cytotoxicity		[17]
In vitro	Fucoxanthin	*Cladosiphon okamuranus Tokida*	Raji, Daudi, B95-8/Ramos	5 μM; 24 h	Induction of apoptosis		[20]
			Daudi, KM-H2, L540	2.5 μM; 24 h	Induction of cell cycle arrest		
			Raji, Daudi, B95-8/Ramos	2.5 μM; 24 h	Induction of apoptosis		
			Daudi, KM-H2, L540	1.25 μM; 24 h	Induction of cell cycle arrest		
In vitro	Fucoxanthinol	*Cladosiphon okamuranus* Tokida	Daudi	0.63, 1.25, 2.5, 5 μM; 24 h	Induction of apoptosis and cell cycle arrest	↑ c-PARP, c-caspase-3, -9 ↓ Bcl-2, cIAP-2, XIAP, cyclin D1, cyclin D2, NF-κB-DNA binding	[20]
In vitro	Fuxocanthinol	*Cladosiphon okamuranus Tokida*	BCBL-1, TY-1	1.3, 2.5, 5 μM; 24 h	Induction of apoptosis	↑ c-PARP, c-caspase-3, -8, -9	[38]
			BCBL-1	1.3, 2.5, 5 μM; 24 h	Induction of cell cycle arrest	↓ Bcl-xL, XIAP, survivin, p-pRb, cyclin D2, CDK4, CDK6, c-Myc, p-IKK β, p-IkB α, IKK α, IKK β, IKK γ, Akt, PDK1, p-cas9, β-catenin, JunB, JunD, NF-κB-DNA	

System	Compound	Source	Cell Line/Animal Model	Dose; Duration	Efficacy	Mechanism	Reference
						binding activity, AP-1 binding	
In vitro	Heraclenin	*Ducrosia anethifolia*	L5178Y PAR	IC50 32.73 μM	Inhibition of proliferation		[20]
			L5178Y MDR	IC50 46.54 μM			
	Heraclenol	*Ducrosia anethifolia*	L5178Y PAR	IC50 52.31 μM	Inhibition of proliferation		
			L5178Y MDR	IC50 46.57 μM			
In vitro	Hydroxyamorphispironone	*Amorpha fruticosa*	L5178Y	IC50 1.3 μM	Induction of cytotoxicity		[17]
In vitro	Imperatorin	*Ducrosia anethifolia*	L5178Y PAR	IC50 36.12 μM	Inhibition of proliferation		[20]
			L5178Y MDR	IC50 42.24 μM			
	Isogospherol	*Ducrosia anethifolia*	L5178Y PAR	IC50 46.53 μM	Inhibition of proliferation		
			L5178Y MDR	IC50 48.75 μM			
In vitro	Isotylocrebrine	*Citrus tachibana* (Makino) T. Tanaka	MT-1	EC50 48.3 nM; 4 h	Inhibition of proliferation		[21]
			MT-2	EC50 25.4 nM; 4 h			
			MT-2	EC50 13.0 nM; 4 h			
In vitro	Isotylocrebrine Noxide	*Citrus tachibana* (Makino) T. Tanaka	MT-1	EC50 379.5 nM; 4 h			[21]
			MT-2	EC50 246.7 nM; 4 h			

System	Compound	Source	Cell Line/Animal Model	Dose; Duration	Efficacy	Mechanism	Reference
In vitro	Methyl angolensate	*Soymida febrifuga*	Daudi	10, 50, 100, 250 µM; 24, 48, 72 h	Inhibition of proliferation Activation of apoptosis ROS formation	↑ c-PARP, MRE11, RAD50, NBS1, p-ATM, KU70, KU80 ↓ p53, p73	[22]
In vitro	Oxypeucedanin	*Ducrosia anethifolia*	L5178Y PAR	IC50 25.98 µM	Inhibition of proliferation		[20]
			L5178Y MDR	IC50 28.89 µM			
	Oxypeucedanin methanolate	*Ducrosia anethifolia*	L5178Y MDR	IC50 35.88 µM	Inhibition of proliferation		
			L5178Y PAR	IC50 33.23 µM			
	Pabulenol	*Ducrosia anethifolia*	L5178Y MDR	IC50 30.47 µM	Inhibition of proliferation		
			L5178Y PAR	IC50 29.28 µM			
In vitro	Peperobtusin A	*Peperomia tetraphylla*	U937	25, 50, 75, 100 µM; 1, 3, 6, 24	Induction of cell cycle arrest and apoptosis	↑ ROS, Bax, c-caspase-8, -9, -3, p-p38 ↓ MMP, Bcl-2, Bid, caspase-3, p38	[24]
In vitro	Psilostachyin C	*Ambrosia* spp.	BW5147	10 µg/mL; 24 h	Induction of apoptosis, necrosis Cell arrest in S phage Inhibition of cell viability, cell proliferation	↓ SOD, CAT, Px	[25]
In vitro	Resveratrol	Various plants	Ramos	20, 50, 70, 100 µM; 1, 3, 6, 10, 24 h	Induction of antiproliferative and proapoptotic activity	↑ c-caspase-3, c-PARP, NOXA, PUMA, p-ATM, p-	[26]

System	Compound	Source	Cell Line/Animal Model	Dose; Duration	Efficacy	Mechanism	Reference
						BRCA1, γ-H2AX, Rad 50, Mre 11, p-p95, DNA-PKcs, KU80 ↓ TCL-1. Myc, Bach2	
In vitro	Resveratrol	Various plants	SNT-8, SNK-10, SNT-16	25 μM; 0.5, 1, 3, 6, 12, 24, 48 h	Induction of cell cycle arrest	↓ Cyclin A2	[27]
					Induction of DNA damage response and apoptosis Inhibition of proliferation	↑ pATM, γ-H2A.X., p-Chk2, p-p53, Bax, Bad, c-caspase-9, -3 ↓ Mcl-1, survivin, p-AKT, p-Stat3	
In vitro	Rotenone	*Amorpha fruticosa*	L5178Y	IC50 0.3 μM	Induction of cytotoxicity		[17]
	rot-2′-enonic acid	*Amorpha fruticosa*	L5178Y	IC50 0.6 μM	Induction of cytotoxicity		[17]
In vitro	Schweinfurthin	*Macaranga alnifolia* Baker	WSU-DLCL2	100 nM; 24 h	Inhibition of proliferation	↑ p-EIF2a ↓ mTOR, AKT	[28]
In vitro	Sermundone	*Amorpha fruticosa*	L5178Y	IC50 0.2 μM	Induction of cytotoxicity		[17]
In vitro	Thymoquinone	*Nigella sativa*	BC-1	10, 25 μM; 24 h	Induction of apoptosis Increase ROS generation Loss of MMP	↑ Bax, c-caspase-3, -9, c-PARP, DR5 ↓ Bcl-2, p-AKT, p-FOXO1, p-GSK3, p-Bad	[30]
			BC-3		Induction of apoptosis, ROS generation	↑ Bax, c-caspase-3, -9, c-PARP ↓ Bcl-2, p-AKT, p-	

System	Compound	Source	Cell Line/Animal Model	Dose; Duration	Efficacy	Mechanism	Reference
						FOXO1, p-GSK3, p-Bad	
			BCBL-1		Induction of apoptosis, ROS generation	↓ p-AKT, p-FOXO1, p-GSK3, p-Bad	
			HBL-6		Induction of apoptosis		
In vitro	Thymoquinone	*Nigella sativa* Linn.	ABC-DLBCL (HBL-1, RIVA)	5, 10 mM; 24 h	Induction of ROS and apoptosis Inhibition of cell viability	↑ c-caspase-9, -3, PARP, Bax ↓ NF-κB, IκBa, Bcl-2, Bcl-Xl, XIAP, Survivin, translocation of p65 subunit of NF-κB, p-p65	[29]
In vitro	Tylophorine N-oxide	*Citrus tachibana* (Makino) T. Tanaka	MT-1	EC50 1590.0 nM; 4 h	Inhibition of proliferation		[22]
			MT-2	EC50 1490.0 nM; 4 h			
In vitro	Tylophorinine N-oxide	*Citrus tachibana* (Makino) T. Tanaka	MT-1	(1)EC50 28.8 nM; 4 h	Inhibition of proliferation		[22]
			MT-2	(2)EC50 4.8 nM; 4 h			
In vitro	3-demethyl-14b-hydroxyisotylocrebrine	*Citrus tachibana* (Makino) T. Tanaka	MT-1	(1)EC50 2.8 nM; 4 h	Inhibition of proliferation		[22]
			MT-2	(2)EC50 2.6 nM; 4 h			
In vitro	3, 3′, 4-tri-O-methylellagic acid	*Combretum dolichopetalum*	L5179Y	IC50 29.0 μM	Induction of cytotoxicity		[15]

System	Compound	Source	Cell Line/Animal Model	Dose; Duration	Efficacy	Mechanism	Reference
In vitro	4-Deoxyraputindole C	*Raputia praetermissa*	Raji	20, 40, 60, 80, 100 μM; 6, 12, 24 h	Induction of cell death	↑ mitochondrial superoxide ↓ MMP, cathepsin B/L	[31]
In vitro	6a,12a- dehydrodeguelin	*Amorpha fruticosa*	L5178Y	IC50 10.2 μM	Induction of cytotoxicity		[17]
	6′-O-β-D-Glucopyranosyldalpanol	*Amorpha fruticosa*	L5178Y	IC50 1.7 μM	Induction of cytotoxicity		[17]
In vitro	14-hydroxytylophorine N-oxide	*Citrus tachibana* (Makino) T. Tanaka	MT-1	EC50 69.8 nM; 4 h	Inhibition of proliferation		[22]
			MT-2	EC50 26.8 nM; 4 h			
In vitro	α-toxicarol	*Amorpha fruticosa*	L5178Y	IC50 0.2 μM	Induction of cytotoxicity		[17]
In vitro	β-Asarone		Raji	100, 200, 400 μM; 72 h	Induction of apoptosis	↑ c-caspase-9, -3, c-PARP ↓ procaspase-9, -3, PARP	[32]
				100 μM	Induction of anticancer effects	↓ NF-κB/p65, p-NF-κB/p65, NF-κB/p65 nuclear translocation	
In vitro	β-Phenethyl isothiocyanate (PEITC)		Raji	10 μM; 3 h	Reduction in mitochondrial respiration rate Increase in cellular H_2O_2 levels Rapid depletion of cellular and mitochondrial glutathione	↓ NDUFS3	[33]
In vitro	(þ)-Oxypeucedanin hydrate	*Ducrosia anethifolia*	L5178Y MDR	IC50 41.96	Inhibition of proliferation		[21]

System	Compound	Source	Cell Line/Animal Model	Dose; Duration	Efficacy	Mechanism	Reference
				μM			
			L5178Y PAR	IC50 60.58 μM			
	Compound 6	[41]	L5178Y	IC50 11.38 μM; 24 h			
	Compound 8		L5178Y	IC50 63.91 μM; 24 h			
	Compound 9		[42] L5178Y	IC50 35.56 μM; 24 h			
In vitro	Compound 10	*Tabernaemontana elegans* Stapf	L5178Y	IC50 29.21 μM; 24 h	Induction of cytotoxicity [43]		[34]
	Compound 15		L5178Y	IC50 34.28 μM; 24 h			
	Compound 16	2+	L5178Y	IC50 20.77 μM; 24 h			
	Compound 23		L5178Y	IC50 33.30 μM; 24 h			
In vitro and in vivo	Chelerythrine	*Chelidonium majus.* L.	BALB/c (H2d) mice	1.25, 2.5 mg/kg; 34 d	Increase in survival duration Inhibition of Dalton's Lymphoma cell growth	[44]	[35]
			TANK	2.5 mg/kg		↑ NKG2D ↓ NKG2A	
In vitro and in vivo	Elatol		SU-DHL-6, OCI-Ly3, RIVA	500 nM, 1, 10 μM; 24, 48, 72, 96 h	[45] Induction of apoptosis		[36]
			SU-DHL-6, OCI-Ly3	5 μM; 16 h		↓ cyclinD3, MYC, MCL1, PIM2	
	[46]			1, 10 μM; 4, 16, 24 h	Inhibition of protein synthesis		

Annomontine, ingenines A, and B are alkalc methanol extract of *Acanthostrongylophora* [41]. Table 3).

proteins such as LC3B-I/II but apoptosis relating proteins in BL cells [44]. Cinobufotalin, known to one of toad venom components has been reported to have anticancer effects in various cancer cell lines including esophageal squamous cell carcinoma and the melanoma cell line [47][48]. This anticancer effect was also observed in U937-a lymphoma cell line [43]. Cinobufotalin induced changes in intracellular Ca^{2+}, MMP and expression of apoptosis relating proteins such as Fas, caspase, Bid, and Bax. Marin sponge derived compounds, (+)-jasplakinolide Z6, (+)-jasplakinolide, (+)-jasplakinolide Z5, and (+)-jasplakinolide V, showed cytotoxicity against L5178Y [46]. These compounds exhibited prominent IC50 values of less than 100 nM except for (+)-jasplakinolide Z6.

Table 3. Animal-derived compounds and lymphoma.

Compound	Source	Cell Line/Animal Model	Dose; Duration	Efficacy	Mechanism	Reference
Annomontine	*Acanthostrongylophoraingens*	L5178Y	ED50 7.8 µg/mL	Induction of cytotoxicity		[41]
Cinachylenic Acid A, B, C, D	*Cinachyrella* sp.	L5178Y	IC50 0.3 µM	Induction of cytotoxicity		[42]
Cinobufotalin	Toad	U937	0.5, 1 µM; 6, 12, 24 h	Decrease in cell viability and MMP Rapid release of cytosolic superoxide anion, increase in intracellular [Ca^{2+}]	↑ Fas, c-caspase-3, -8 ↓ Pro-caspase-2, -3, -8, -9, cytosolic Bid, cytosolic Bax	[43]
Frondoside A	*Cucumaria frondosa*	CA46, Namalwa, Ramos, BL-2	0.3, 0.6 µM; 48 h	Induction of cell cycle arrest		[44]
		CA46	0.3 µM; 48 h	Inhibition of prosurvival autophagy	↑ LC3B-I/II, SQSTM1/p62	
			0.3, 0.6 µM; 48 h	Induction of apoptosis	↑ c-PARP ↓ Survivin, Bcl-2	
		CA46, BL-2, Ramos	0.3, 0.6 µM ;48 h	Induction of apoptosis	↑ Cyt C, AIF, HtrA2/Omi	
Ingenine B	*Acanthostrongylophoraingens*	L5178Y	ED50 9.1 µg/mL	Induction of cytotoxicity		[41]
Iodocionin	*Ciona edwardsii*	L5178Y	0.1, 0.3, 1, 3, 10 µg/mL; 72 h	Inhibition of cell proliferation		[45]

Compound	Source	Cell Line/Animal Model	Dose; Duration	Efficacy	Mechanism	Reference
(+)-Jasplakinolide. (+)-Jasplakinolide Z5, (+)-Jasplakinolide V	*Jaspis splendens*	L5178Y	IC50 < 100 nM	Induction of cytotoxicity		[46]
(+)-Jasplakinolide Z6			IC50 3.2 μM			
		γc^{null} mice/EL4	mg/kg; 38 days	Increase in survival time		
		Daudi, Namalwa, SU-DHL-4, SU-DHL-2	5, 7, 10 μM; 24 h	Induction of apoptosis		
		SU-DHL-2, NAMALWA			↑ c-PARP, c-caspase-3	
		Daudi, NAMALWA, SU-DHL-2	5, 10 μM; 6 h		↓ cyclin D1, Bcl-2, IκBα,	
In vitro and in vivo	11(13)-dehydroivaxillin	*Carpesium genus*	10 μM; 4 h		↓ p-IκBα, p-p65	[40]
		Daudi, SU-DHL-2	5, 7 μM; 24 h		↓ IKKα/IKKβ, c-MYC, cyclinD1, NF-κB	
		B-NSG mice(Daudi, SU-DHL-2 xenograft)	50 mg/kg; 10 days	Inhibition of tumor growth	↓ IKKα/IKKβ, PCNA	

7. Özkaya, F.C.; Ebrahim, W.; El-Neketi, M.; Tansel Tanrıkul, T.; Kalscheuer, R.; Müller, W.E.G.; Guo, Z.; Zou, K.; Liu, Z.; Proksch, P. Induction of new metabolites from sponge-associated fungus Aspergillus carneus by OSMAC approach. Fitoterapia 2018, 131, 9–14, doi:10.1016/j.fitote.2018.10.008.
8. Frank, M.; Hartmann, R.; Plenker, M.; Mándi, A.; Kurtán, T.; Özkaya, F.C.; Müller, W.E.G.; Kassack, M.U.; Hamacher, A.; Lin, W.; et al. Brominated Azaphilones from the Sponge-Associated Fungus Penicillium canescens Strain 4.14.6a. J. Nat. Prod. 2019, 82, 2159–2166, doi:10.1021/acs.jnatprod.9b00151.
9. Lai, D.; Brötz-Oesterhelt, H.; Müller, W.E.G.; Wray, V.; Proksch, P. Bioactive polyketides and alkaloids from Penicillium citrinum, a fungal endophyte isolated from Ocimum tenuiflorum. Fitoterapia 2013, 91, 100–106, doi:10.1016/j.fitote.2013.08.017.

Cleaved poly ADP ribose polymerase (c-PARP); cleaved caspase (c-caspase); procaspase (p-caspase); reactive oxygen species (ROS); superoxide dismutase (SOD); catalase (CAT); peroxidase (Px); death receptor (DR); mitochondrial membrane potential (MMP); X-linked inhibitor of apoptosis protein (XIAP); B-cell lymphoma-extra large (Bcl-xL); retinoblastoma protein (Rb); IκB kinase (IKK); phosphoinositide dependent protein kinase (PDK); nuclear factor kappa B (NFκB); activator protein (AP); cellular inhibitor of apoptosis protein (cIAP); forkhead box

10. El-Neketi, M.; Ebrahim, W.; Lin, W.; Gedara, S.; Badria, F.A.; Saad, H.E.; Lai, D.; Proksch, P. Alkaloids and cytotoxic sterols from Penicillium citrinum, an endophyte isolated from the Mediterranean plant Cleome arabica L. Nat. Prod. Res. 2013, 27, 1099–1104, doi:10.1021/np400366

protein kinase (PKC); glycogen synthase kinase (GSK); proliferating cell nuclear antigen (PCNA); glucose-regulated protein (GRP); tumor necrosis factor (TNF); tetradecanoyl phorbol acetate (TPA); extracellular signal-regulated kinase (ERK); activating transcription factor (ATF); cyclin dependent kinase (CDK); phosphatidylinositol 3-kinase (PI3K); sirtuin (SIRT); DNA dependent protein kinase (DNA PK); signal transducer and activator of transcription (STAT); p53 upregulated modulator of apoptosis (PUMA); checkpoint kinase (Chk); death receptor (DR).

11. Liu, Y.; Kurtán, T.; Yun Wang, C.; Han Lin, W.; Orfali, R.; Müller, W.E.; Daletos, G.; Proksch, P. Cladosporinone, a new viriditoxin derivative from the hypersaline lake derived fungus Cladosporium cladosporioides. J. Antibiot. 2016, 69, 702–706, doi:10.1038/ja.2016.11.

12. Abdel-Wahab, N.M.; Harwoko, H.; Müller, W.E.G.; Hamacher, A.; Kassack, M.U.; Fouad, M.A.; Kamel, M.S.; Lin, W.; Ebrahim, W.; Liu, Z.; et al. Cyclic heptapeptides from the soil-derived fungus Clonostachys rosea. Bioorganic Med. Chem. 2019, 27, 3954–3959, doi:10.1016/j.bmc.2019.07.025.

13. Yu, X.; Müller, W.E.; Guo, Z.; Lin, W.; Zou, K.; Liu, Z.; Proksch, P. Indole alkaloids from the coprophilous fungus Aphanoascus fulvescens. Fitoterapia 2019, 136, 104168.

14. Umeokoli, B.O.; Ebrahim, W.; El-Neketi, M.; Müller, W.E.G.; Kalscheuer, R.; Lin, W.; Liu, Z.; Proksch, P. A new depsidone derivative from mangrove sediment derived fungus Lasiodiplodia theobromae. Nat. Prod. Res. 2019, 33, 2215–2222, doi:10.1080/14786419.2018.1496430.

15. Uzor, P.F.; Ebrahim, W.; Osadebe, P.O.; Nwodo, J.N.; Okoye, F.B.; Müller, W.E.; Lin, W.; Liu, Z.; Proksch, P. Metabolites from Combretum dolichopetalum and its associated endophytic fungus Nigrospora oryzae--Evidence for a metabolic partnership. Fitoterapia 2015, 105, 147–150, doi:10.1016/j.fitote.2015.06.018.

16. Niveshika; Verma, E.; Maurya, S.K.; Mishra, R.; Mishra, A.K. The Combined Use of in Silico, in Vitro, and in Vivo Analyses to Assess Anti-cancerous Potential of a Bioactive Compound from Cyanobacterium Nostoc sp. MGL001. Front. Pharm. 2017, 8, 873, doi:10.3389/fphar.2017.00873.

17. Muharini, R.; Díaz, A.; Ebrahim, W.; Mándi, A.; Kurtán, T.; Rehberg, N.; Kalscheuer, R.; Hartmann, R.; Orfali, R.S.; Lin, W.; et al. Antibacterial and Cytotoxic Phenolic Metabolites from the Fruits of Amorpha fruticosa. J. Nat. Prod. 2017, 80, 169–180, doi:10.1021/acs.jnatprod.6b00809.

18. Baba, Y.; Shigemi, Z.; Hara, N.; Moriguchi, M.; Ikeda, M.; Watanabe, T.; Fujimuro, M. Arctigenin induces the apoptosis of primary effusion lymphoma cells under conditions of glucose deprivation. Int. J. Oncol. 2018, 52, 505–517, doi:10.3892/ijo.2017.4215.

19. Zhao, Q.; Guan, J.; Qin, Y.; Ren, P.; Zhang, Z.; Lv, J.; Sun, S.; Zhang, C.; Mao, W. Curcumin sensitizes lymphoma cells to DNA damage agents through regulating Rad51-dependent homologous recombination. Biomed. Pharm. 2018, 97, 115–119, doi:10.1016/j.biopha.2017.09.078.

20. Tafuku, S.; Ishikawa, C.; Yasumoto, T.; Mori, N. Anti-neoplastic effects of fucoxanthin and its deacetylated product, fucoxanthinol, on Burkitt's and Hodgkin's lymphoma cells. Oncol. Rep. 2012, 28, 1512–1518, doi:10.3892/or.2012.1947.

21. Mottaghipisheh, J.; Nové, M.; Spengler, G.; Kúsz, N.; Hohmann, J.; Csupor, D. Antiproliferative and cytotoxic activities of furocoumarins of Ducrosia anethifolia. Pharm. Biol. 2018, 56, 658–664, doi:10.1080/13880209.2018.1548625.
22. Nakano, D.; Ishitsuka, K.; Ikeda, M.; Tsuchihashi, R.; Okawa, M.; Okabe, H.; Tamura, K.; Kinjo, J. Screening of promising chemotherapeutic candidates from plants against human adult T-cell leukemia/lymphoma (IV): Phenanthroindolizidine alkaloids from Tylophora tanakae leaves. J. Nat. Med. 2015, 69, 397–401, doi:10.1007/s11418-015-0906-8.
23. Chiruvella, K.K.; Raghavan, S.C. A natural compound, methyl angolensate, induces mitochondrial pathway of apoptosis in Daudi cells. Investig. New Drugs 2011, 29, 583–592, doi:10.1007/s10637-010-9393-7.
24. Shi, L.; Qin, H.; Jin, X.; Yang, X.; Lu, X.; Wang, H.; Wang, R.; Yu, D.; Feng, B. The natural phenolic peperobtusin A induces apoptosis of lymphoma U937 cells via the Caspase dependent and p38 MAPK signaling pathways. Biomed. Pharm. 2018, 102, 772–781, doi:10.1016/j.biopha.2018.03.141.
25. Martino, R.; Beer, M.F.; Elso, O.; Donadel, O.; Sülsen, V.; Anesini, C. Sesquiterpene lactones from Ambrosia spp. are active against a murine lymphoma cell line by inducing apoptosis and cell cycle arrest. Toxicol. Vitr. 2015, 29, 1529–1536, doi:10.1016/j.tiv.2015.06.011.
26. Jara, P.; Spies, J.; Cárcamo, C.; Arancibia, Y.; Vargas, G.; Martin, C.; Salas, M.; Otth, C.; Zambrano, A. The Effect of Resveratrol on Cell Viability in the Burkitt's Lymphoma Cell Line Ramos. Molecules 2017, 23, 14, doi:10.3390/molecules23010014.
27. Sui, X.; Zhang, C.; Zhou, J.; Cao, S.; Xu, C.; Tang, F.; Zhi, X.; Chen, B.; Wang, S.; Yin, L. Resveratrol inhibits Extranodal NK/T cell lymphoma through activation of DNA damage response pathway. J. Exp. Clin. Cancer Res. 2017, 36, 133, doi:10.1186/s13046-017-0601-6.
28. Bao, X.; Zheng, W.; Hata Sugi, N.; Agarwala, K.L.; Xu, Q.; Wang, Z.; Tendyke, K.; Lee, W.; Parent, L.; Li, W.; et al. Small molecule schweinfurthins selectively inhibit cancer cell proliferation and mTOR/AKT signaling by interfering with trans-Golgi-network trafficking. Cancer Biol. Ther. 2015, 16, 589–601, doi:10.1080/15384047.2015.1019184.
29. Hussain, A.R.; Uddin, S.; Ahmed, M.; Al-Dayel, F.; Bavi, P.P.; Al-Kuraya, K.S. Phosphorylated IκBα predicts poor prognosis in activated B-cell lymphoma and its inhibition with thymoquinone induces apoptosis via ROS release. PLoS ONE 2013, 8, e60540, doi:10.1371/journal.pone.0060540.
30. Hussain, A.R.; Ahmed, M.; Ahmed, S.; Manogaran, P.; Platanias, L.C.; Alvi, S.N.; Al-Kuraya, K.S.; Uddin, S. Thymoquinone suppresses growth and induces apoptosis via generation of reactive oxygen species in primary effusion lymphoma. Free Radic. Biol. Med. 2011, 50, 978–987, doi:10.1016/j.freeradbiomed.2010.12.034.

31. Vital, W.D.; Torquato, H.F.V.; Jesus, L.O.P.; Judice, W.A.S.; Silva, M.; Rodrigues, T.; Justo, G.Z.; Veiga, T.A.M.; Paredes-Gamero, E.J. 4-Deoxyraputindole C induces cell death and cell cycle arrest in tumor cell lines. J. Cell. Biochem. 2019, 120, 9608–9623, doi:10.1002/jcb.28238.
32. Lv, L.N.; Wang, X.C.; Tao, L.J.; Li, H.W.; Li, S.Y.; Zheng, F.M. β-Asarone increases doxorubicin sensitivity by suppressing NF-κB signaling and abolishes doxorubicin-induced enrichment of stem-like population by destabilizing Bmi1. Cancer Cell Int. 2019, 19, 153, doi:10.1186/s12935-019-0873-3.
33. Chen, G.; Chen, Z.; Hu, Y.; Huang, P. Inhibition of mitochondrial respiration and rapid depletion of mitochondrial glutathione by β-phenethyl isothiocyanate: Mechanisms for anti-leukemia activity. Antioxid Redox Signal. 2011, 15, 2911–2921, doi:10.1089/ars.2011.4170.
34. Paterna, A.; Kincses, A.; Spengler, G.; Mulhovo, S.; Molnár, J.; Ferreira, M.U. Dregamine and tabernaemontanine derivatives as ABCB1 modulators on resistant cancer cells. Eur. J. Med. Chem. 2017, 128, 247–257, doi:10.1016/j.ejmech.2017.01.044.
35. Kumar, S.; Tomar, M.S.; Acharya, A. Chelerythrine delayed tumor growth and increased survival duration of Dalton's lymphoma bearing BALB/c H(2d) mice by activation of NK cells in vivo. J. Cancer Res. Ther. 2015, 11, 904–910, doi:10.4103/0973-1482.143342.
36. Peters, T.L.; Tillotson, J.; Yeomans, A.M.; Wilmore, S.; Lemm, E.; Jiménez-Romero, C.; Amador, L.A.; Li, L.; Amin, A.D.; Pongtornpipat, P.; et al. Target-Based Screening against eIF4A1 Reveals the Marine Natural Product Elatol as a Novel Inhibitor of Translation Initiation with In Vivo Antitumor Activity. Clin. Cancer Res. 2018, 24, 4256–4270, doi:10.1158/1078-0432.Ccr-17-3645.
37. Yamamoto, K.; Ishikawa, C.; Katano, H.; Yasumoto, T.; Mori, N. Fucoxanthin and its deacetylated product, fucoxanthinol, induce apoptosis of primary effusion lymphomas. Cancer Lett. 2011, 300, 225–234, doi:10.1016/j.canlet.2010.10.016.
38. Yu, D.; Zhang, Y.; Chen, G.; Xie, Y.; Xu, Z.; Chang, S.; Hu, L.; Li, B.; Bu, W.; Wang, Y.; et al. Targeting the PI3K/Akt/mTOR signaling pathway by pterostilbene attenuates mantle cell lymphoma progression. Acta Biochim. Biophys. Sin. 2018, 50, 782–792, doi:10.1093/abbs/gmy070.
39. Singh, N.P.; Singh, U.P.; Hegde, V.L.; Guan, H.; Hofseth, L.; Nagarkatti, M.; Nagarkatti, P.S. Resveratrol (trans-3,5,4'-trihydroxystilbene) suppresses EL4 tumor growth by induction of apoptosis involving reciprocal regulation of SIRT1 and NF-κB. Mol. Nutr. Food Res. 2011, 55, 1207–1218, doi:10.1002/mnfr.201000576.
40. Xiao, X.; Li, H.; Jin, H.; Jin, J.; Yu, M.; Ma, C.; Tong, Y.; Zhou, L.; Lei, H.; Xu, H.; et al. Identification of 11(13)-dehydroivaxillin as a potent therapeutic agent against non-Hodgkin's lymphoma. Cell Death Dis. 2017, 8, e3050, doi:10.1038/cddis.2017.442.

41. Ibrahim, S.R.; Mohamed, G.A.; Zayed, M.F.; Sayed, H.M. Ingenines A and B, Two New Alkaloids from the Indonesian Sponge Acanthostrongylophora ingens. Drug Res. 2015, 65, 361–365, doi:10.1055/s-0034-1384577.
42. Mokhlesi, A.; Hartmann, R.; Kurtán, T.; Weber, H.; Lin, W.; Chaidir, C.; Müller, W.E.G.; Daletos, G.; Proksch, P. New 2-Methoxy Acetylenic Acids and Pyrazole Alkaloids from the Marine Sponge Cinachyrella sp. Mar. Drugs 2017, 15, 356, doi:10.3390/md15110356.
43. Emam, H.; Zhao, Q.L.; Furusawa, Y.; Refaat, A.; Ahmed, K.; Kadowaki, M.; Kondo, T. Apoptotic cell death by the novel natural compound, cinobufotalin. Chem. Biol. Interact. 2012, 199, 154–160, doi:10.1016/j.cbi.2012.07.005.
44. Dyshlovoy, S.A.; Rast, S.; Hauschild, J.; Otte, K.; Alsdorf, W.H.; Madanchi, R.; Kalinin, V.I.; Silchenko, A.S.; Avilov, S.A.; Dierlamm, J.; et al. Frondoside A induces AIF-associated caspase-independent apoptosis in Burkitt lymphoma cells. Leuk. Lymphoma 2017, 58, 2905–2915, doi:10.1080/10428194.2017.1317091.
45. Aiello, A.; Fattorusso, E.; Imperatore, C.; Menna, M.; Müller, W.E. Iodocionin, a cytotoxic iodinated metabolite from the Mediterranean ascidian Ciona edwardsii. Mar. Drugs 2010, 8, 285–291, doi:10.3390/md8020285.
46. Ebada, S.S.; Müller, W.E.G.; Lin, W.; Proksch, P. New Acyclic Cytotoxic Jasplakinolide Derivative from the Marine Sponge Jaspis splendens. Mar. Drugs 2019, 17, 100, doi:10.3390/md17020100.
47. Pan, Z.; Qu, C.; Chen, Y.; Chen, X.; Liu, X.; Hao, W.; Xu, W.; Ye, L.; Lu, P.; Li, D.; et al. Bufotalin induces cell cycle arrest and cell apoptosis in human malignant melanoma A375 cells. Oncol. Rep. 2019, 41, 2409–2417, doi:10.3892/or.2019.7032.
48. Lin, S.; Lv, J.; Peng, P.; Cai, C.; Deng, J.; Deng, H.; Li, X.; Tang, X. Bufadienolides induce p53-mediated apoptosis in esophageal squamous cell carcinoma cells in vitro and in vivo. Oncol. Lett. 2018, 15, 1566–1572, doi:10.3892/ol.2017.7457.