

# 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.

Keywords: 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 <sup>[1][2]</sup> (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 <sup>[3]</sup>. Several natural compounds from *Aspergillus fumigatus* YK-7 significantly inhibited growth of U937 cells after three days of treatment; the natural compounds included pyripropene E, alismol, helvolic acid, and  $\beta$ -5, 8, 11-trihydroxybergamot-9-ene <sup>[4]</sup>. 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* <sup>[5]</sup>. Among the compounds, aluminiumneohydroxyaspergillin exhibited cytotoxicity against the U937 cell line (IC<sub>50</sub> = 4.2  $\mu$ M). L. Hammerschmidt et al. isolated twelve compounds from *Gymnascella dankaliensis* ethyl acetate extract and measured their cytotoxicity against the L5178Y cell line <sup>[6]</sup>. Four compounds were found to have cytotoxicity. Aranorosin-2-methylether, aranorosin, and gymnastatin A showed potent cytotoxic activity against L5178Y cells with IC<sub>50</sub> values of 0.44, 0.58, and 0.64  $\mu$ M, respectively. Gymnastatin B had moderate cytotoxic activity with an IC<sub>50</sub> value of 5.8  $\mu$ M. Three natural products isolated from *Aspergillus carneus*, isopropylchetominine, sterigmatocystin, and astelotoxin E showed significant cytotoxicity against mouse lymphoma cell L5178Y (IC<sub>50</sub> 0.04, 0.3, and 0.2  $\mu$ M, respectively) <sup>[7]</sup>. Bromophilone B isolated from sponge-associated fungus *Penicillium canescens* displayed cytotoxicity against L5178Y, a mouse lymphoma cell line (IC<sub>50</sub> 8.9  $\mu$ M) <sup>[8]</sup>. *Penicillium citrinum* var. originated natural compounds, including 5-methyl alternariol ether, methyl, 8-hydroxy-6-methyl-9-oxo-9H-xanthen-1-carboxylate, and citriquinochroman, showed toxic events against L5178Y cells each at doses of IC<sub>50</sub> 0.78, 1.0  $\mu$ g/mL, IC<sub>50</sub> 0.78, 1.0  $\mu$ g/ml, and IC<sub>50</sub> 6.1  $\mu$ M <sup>[9][10]</sup>. Cladosporinone and viriditoxin which are derived from *Cladosporium Cladosporioides* (Fresen). G.A. de Vries also induced cytotoxicity when administered to L5178Y cells in IC<sub>50</sub> 0.88 and 0.1  $\mu$ M <sup>[11]</sup>. Verticillin D and new cyclic heptapeptides Cyclo-(Gly-D-Leu-D-allo-Ile-L-Val-L-Val-D-Trp- $\beta$ -Ala) isolated from soil-derived fungus *Clonostachys rosea* displayed significant cytotoxicity against L5178Y mouse lymphoma cell lines (IC<sub>50</sub> 0.1 and 4.1  $\mu$ M, respectively) <sup>[12]</sup>. Yu et al. investigated metabolites from ascomycete fungus *Aphanoascus fulvescens* isolated from goose dung <sup>[13]</sup>. Indole alkaloids, okaramine A, C, G, and H were evaluated to induce cytotoxicity against L5178Y cell lines at different IC<sub>50</sub> concentrations, among which okaramine G showed the highest significance. Umeokoli et al. isolated 9 compounds from *Lasiodiplodia theobromae* M4.2-2 <sup>[14]</sup>. 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 (IC<sub>50</sub> = 7.3  $\mu$ M). P.F. Uzor et al. isolated three compounds from the fungus *Nigrospora oryzae* and six compounds from its host plant, *Combretum dolichopetalum* <sup>[15]</sup>. 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 IC<sub>50</sub> value 9.4  $\mu$ M, and 3, 3', 4-tri-O-methylellagic acid from *Combretum dolichopetalum* methanol extract showed the IC<sub>50</sub> value of 29.0  $\mu$ M. 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 IC<sub>50</sub> value <sup>[16]</sup>. As shown in Table 1, twenty-seven compounds from microorganism exert cytotoxicity against lymphoma cell lines. Among them, Alismol, Helvolic acid, and  $\beta$ -5,8,11-

trihydroxybergemot-9-ene from *Aspergillus fumigatus* YK-7 had IC50 values more than 50  $\mu\text{M}$ , but several compounds, including aranorosin and gymnastatin A from *Gymnascella dankaliensis*, were less than 1  $\mu\text{M}$  [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  | <i>Aspergillus fumigatus</i> YK-7                                    | U937                   | IC50 67.1 $\mu\text{M}$ ; 3 days | Inhibition of proliferation | [4]       |
| aluminiumneohydroxyaspergillin                               | Co-culture of <i>Aspergillus sclerotiorum</i> and <i>Penicillium</i> | U937                   | IC50 4.2 $\mu\text{M}$ ; 48 h    | Induction of cytotoxicity   | [5]       |
| Aranorosin   | <i>Gymnascella dankaliensis</i>                                      | L5178Y                 | IC50 0.58 $\mu\text{M}$          | Induction of cytotoxicity   | [6]       |
| Aranorosin-2-methylether                                     | <i>Gymnascella dankaliensis</i>                                      | L5178Y                 | IC50 0.44 $\mu\text{M}$          | Induction of cytotoxicity   | [6]       |
| Asteltoxin E   | <i>Aspergillus carneus</i>   | L5178Y                 | IC50 0.2 $\mu\text{M}$           | Induction of cytotoxicity   | [7]       |
| Bromophilone B   | <i>Penicillium canescens</i>   | L5178Y                 | IC50 8.9 $\mu\text{M}$           | Induction of cytotoxicity   | [8]       |
| Citriquinochroman  | <i>Penicillium citrinum</i> , var                                    | L5178Y                 | IC50 6.1 $\mu\text{M}$           | Induction of cytotoxicity   | [10]      |
| Cladosporinone   | <i>Cladosporium Cladosporioides</i> (Fresen.) G.A. de Vries          | L5187Y                 | IC50 0.88 $\mu\text{M}$          | Induction of cytotoxicity   | [11]      |
| Cyclo-(Gly-D-Leu-D-allo-Ile-L-Val-L-Val-D-Trp- $\beta$ -Ala) | <i>Clonostachys rosea</i>  | L5178Y                 | IC50 4.1 $\mu\text{M}$           | Induction of cytotoxicity   | [12]      |
| Gymnastatin A  | <i>Gymnascella dankaliensis</i>                                      | L5178Y                 | IC50 0.64 $\mu\text{M}$          | Induction of cytotoxicity   | [7]       |
| Gymnastatin B  | <i>Gymnascella dankaliensis</i>                                      | L5178Y                 | IC50 5.80 $\mu\text{M}$          | Induction of cytotoxicity   | [6]       |
| Helvolic acid  | <i>Aspergillus fumigatus</i> YK-7                                    | U937                   | IC50 57.5 $\mu\text{M}$ ; 3 days | Inhibition of proliferation | [4]       |
| Isopropylchetominine   | <i>Aspergillus carneus</i>   | L5178Y                 | IC50 0.4 $\mu\text{M}$           | Induction of cytotoxicity   | [7]       |
| methyl 8-hydroxy-6-methyl-9-oxo-9H-xanthen-1-carboxylate     | <i>Penicillium citrinum</i> var.                                     | L5178Y                 | IC50 0.78, 1.0 $\mu\text{g/mL}$  | Induction of cytotoxicity   | [9]       |
| Okaramine A  |  |                        | IC50 4.0 $\mu\text{M}$           |                             |           |
| Okaramine C  | <i>Aphanoascus fulvescens</i> (Cooke) Apinis                         | L5178Y                 | IC50 12.8 $\mu\text{M}$          | Induction of cytotoxicity   | [13]      |
| Okaramine G  |  |                        | IC50 13.8 $\mu\text{M}$          |                             |           |
| Okaramine H  |  |                        | IC50 14.7 $\mu\text{M}$          |                             |           |
| Pyripropene E  | <i>Aspergillus fumigatus</i> YK-7                                    | U937                   | IC50 4.2 $\mu\text{M}$ ; 3 days  | Inhibition of proliferation | [4]       |
| Sterigmatocystin   | <i>Aspergillus carneus</i>   | L5178Y                 | IC50 0.3 $\mu\text{M}$           | Induction of cytotoxicity   | [7]       |
| Verticillin D  | <i>Clonostachys rosea</i>  | L5178Y                 | IC50 0.1 $\mu\text{M}$           | Induction of cytotoxicity   | [12]      |
| Viriditoxin  | <i>Cladosporium</i>  | L5187Y                 | IC50 0.1 $\mu\text{M}$           | Inhibition of proliferation | [11]      |

| Compound   | Source                            | Cell Line/Animal Model | Dose; Duration            | Efficacy                    | Reference |
|--|-----------------------------------|------------------------|---------------------------|-----------------------------|-----------|
| 1H-Dibenzo (b, e) (1, 4) dioxepin- 11-one,3, 8- dihydroxy- 4-(methoxymethyl)-1,6-dimethyl        | <i>Lasiodiplodia theobromae</i>   | L5178Y                 | IC50 7.3 $\mu$ M          | Induction of cytotoxicity   | [14]      |
| 4-Dehydroxy-altersolanol A   | <i>Nigrospora oryzae</i>          | L5178Y                 | IC50 9.4 $\mu$ M          | Induction of cytotoxicity   | [15]      |
| 5-methyl alternariol ether   | <i>Penicillium citrinum</i> var.  | L5178Y                 | IC50 0.78, 1.0 $\mu$ g/mL | Induction of cytotoxicity   | [9]       |
| 9-Ethyliminomethyl-12-(morpholin-4-ylmethoxy)-5,8,13,16-tetraaza -hexacene-2,3-dicarboxylic acid | cyanobacterium <i>Nostoc</i> sp.  | DLA                    | IC50 372.4 ng/mL; 24 h    | Induction of cytotoxicity   | [16]      |
| $\beta$ -5,8,11-trihydroxybergamot-9-ene   | <i>Aspergillus fumigatus</i> YK-7 | U937                   | IC50 84.9 $\mu$ M; 3 days | Inhibition of proliferation | [4]       |

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

## 2. Plant-Derived Compounds and Lymphoma

### 2.1. In Vitro Studies

There are several plant-derived compounds that showed an anticancer effect against lymphoma (Table 2). Muharini et al. reported that eleven of fifty-four compounds isolated from *Amorpha fruticosa* induced cytotoxicity against L5178Y mouse lymphoma cells [17]. As shown under the table, the IC50 values of eleven compounds were distributed between 0.2 and 10.2  $\mu$ M, respectively. Baba et al. identified that apoptosis of primary effusion lymphoma (PEL) cells such as BC3, Ramos, BCBL1, and DG75 was induced under glucose-free conditions by 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 6 $\alpha$  (ATF6 $\alpha$ ) 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  $\gamma$ H2AX, 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 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  $\kappa$ B (NF $\kappa$ B)-DNA binding activity was observed in Daudi by using electrophoretic mobility shift assay. These results indicated that FXOH induced apoptosis by decreasing NF $\kappa$ B-DNA binding activity, followed by inhibition of antiapoptotic and cell cycle regulatory proteins. Mottaghpisheh 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, (p)-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  $\mu$ M. 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  $\mu$ M 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<sub>2</sub>O<sub>2</sub> 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. NDUF53, 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 IC<sub>50</sub> 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 G<sub>0</sub>/G<sub>1</sub> 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 caspase-3 and PARP was shown in SU-DHL-2 and NAMALWA 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 FX and 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- $\kappa$ B 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,  $\gamma$ -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 | Amorphispironones B | <i>Amorpha fruticosa</i>             | L5178Y                   | IC50 7.6 $\mu$ M                             | Induction of cytotoxicity             |  | [17]      |   |
|          |                     |                                      | BC3                      | Glucose(-), 5 $\mu$ M; 2, 4, 6 h             |                                       |  |           | $\uparrow$ c-caspase-3, -9, c-PARP                          |
|          |                     |                                      | BC3, Ramos               | Glucose(-), 1, 5, 10 $\mu$ M                 |                                       |  |           | $\downarrow$ MMP, ATP                                       |
| In vitro | Arctigenin          |                                      | BC3, BCBL1               | Glucose(-), 5, 10 $\mu$ M; 3, 4, 6 h         | Induction of apoptosis                | $\uparrow$ GRP94, CHOP<br>$\downarrow$ p-p38, p-ERK1/2, p-p90RSK, GRP78, ATF6 $\alpha$ | [18]      |   |
|          |                     |                                      | Ramos, DG75              | Glucose(-), 5 $\mu$ M, 4, 6 h                |                                       |  |           | $\uparrow$ GRP94, CHOP<br>$\downarrow$ GRP78, ATF6 $\alpha$ |
| In vitro | Curcumin            |                                      | CH12F3                   | 3, 6, 9, 10, 20, 30, 40, 50 $\mu$ M; 4, 24 h | Induction of DNA damage and apoptosis | $\uparrow$ $\gamma$ H2AX, PAPR1, PCNA, caspase-3, -9<br>$\downarrow$ Rad51             | [19]      |   |
| In vitro | Dalbinol            | <i>Amorpha fruticosa</i>             | L5178Y                   | IC50 0.2 $\mu$ M                             | Induction of cytotoxicity             |  | [17]      |   |
|          | Dalpanol            | <i>Amorpha fruticosa</i>             | L5178Y                   | IC50 0.7 $\mu$ M                             | Induction of cytotoxicity             |  | [17]      |   |
|          | Deguelin            | <i>Amorpha fruticosa</i>             | L5178Y                   | IC50 0.2 $\mu$ M                             | Induction of cytotoxicity             |  | [17]      |   |
| In vitro | Fucoxanthin         | <i>Cladosiphon okamuranus</i> Tokida | Raji, Daudi, B95-8/Ramos | 5 $\mu$ M; 24 h                              | Induction of apoptosis                |  | [20]      |   |
|          |                     |                                      | Daudi, KM-H2, L540       | 2.5 $\mu$ M; 24 h                            |                                       |  |           | Induction of cell cycle arrest                              |

| System   | Compound                | Source                                     | Cell Line/Animal Model   | Dose; Duration                   | Efficacy                                     | Mechanism   | Reference |
|----------|-------------------------|--|--------------------------|----------------------------------|--|---|-----------|
| In vitro | Fucoxanthinol           | <i>Cladosiphon okamuranus</i> Tokida       | Raji, Daudi, B95-8/Ramos | 2.5 $\mu$ M; 24 h                | Induction of apoptosis                       | ↑ c-PARP, c-caspase-3, -9<br>↓ Bcl-2, cIAP-2, XIAP, cyclin D1, cyclin D2, NF- $\kappa$ B-DNA binding  | [20]      |
|          |                         |  | Daudi, KM-H2, L540       | 1.25 $\mu$ M; 24 h               | Induction of cell cycle arrest               |   |           |
|          |                         |  | Daudi                    | 0.63, 1.25, 2.5, 5 $\mu$ M; 24 h | Induction of apoptosis and cell cycle arrest |   |           |
| In vitro | Fuxocanthinol           | <i>Cladosiphon okamuranus</i> Tokida       | BCBL-1, TY-1             | 1.3, 2.5, 5 $\mu$ M; 24 h        | Induction of apoptosis                       | ↑ c-PARP, c-caspase-3, -8, -9<br><br>↓ Bcl-xL, XIAP, survivin, p-pRb, cyclin D2, CDK4, CDK6, c-Myc, p-IKK $\beta$ , p-IkB $\alpha$ , IKK $\alpha$ , IKK $\beta$ , IKK $\gamma$ , Akt, PDK1, p-cas9, $\beta$ -catenin, JunB, JunD, NF- $\kappa$ B-DNA binding activity, AP-1 binding | [38]      |
|          |                         |  | BCBL-1                   | 1.3, 2.5, 5 $\mu$ M; 24 h        | Induction of cell cycle arrest               |   |           |
| In vitro | Heraclenin              | <i>Ducrosia anethifolia</i>                | L5178Y PAR               | IC50 32.73 $\mu$ M               | Inhibition of proliferation                  |   | [20]      |
|          |                         |  | L5178Y MDR               | IC50 46.54 $\mu$ M               |  |   |           |
| In vitro | Heraclenol              | <i>Ducrosia anethifolia</i>                | L5178Y PAR               | IC50 52.31 $\mu$ M               | Inhibition of proliferation                  |   | [20]      |
|          |                         |  | L5178Y MDR               | IC50 46.57 $\mu$ M               |  |   |           |
| In vitro | Hydroxyamorphispironone | <i>Amorpha fruticosa</i>                   | L5178Y                   | IC50 1.3 $\mu$ M                 | Induction of cytotoxicity                    |   | [17]      |
| In vitro | Imperatorin             | <i>Ducrosia anethifolia</i>                | L5178Y PAR               | IC50 36.12 $\mu$ M               | Inhibition of proliferation                  |   | [20]      |
|          |                         |  | L5178Y MDR               | IC50 42.24 $\mu$ M               |  |   |           |
| In vitro | Isogospherol            | <i>Ducrosia anethifolia</i>                | L5178Y PAR               | IC50 46.53 $\mu$ M               | Inhibition of proliferation                  |   | [20]      |
|          |                         |  | L5178Y MDR               | IC50 48.75 $\mu$ M               |  |   |           |
| In vitro | Isotylocrebrine         | <i>Citrus tachibana</i> (Makino) T. Tanaka | MT-1                     | EC50 48.3 nM; 4 h                | Inhibition of proliferation                  |   | [21]      |
|          |                         |  | MT-2                     | EC50 25.4 nM; 4 h                |  |   |           |
| In vitro |                         |  | MT-2                     | EC50 13.0 nM; 4 h                |  |   |           |

| System   | Compound                  | Source  | Cell Line/Animal Model | Dose; Duration                                 | Efficacy   | Mechanism  | Reference |
|----------|---------------------------|---|------------------------|--|--|--|-----------|
| In vitro | Isotylocrebrine Noxide    | <i>Citrus tachibana</i> (Makino)<br>T. Tanaka | MT-1                   | EC50<br>379.5 nM;<br>4 h                       |  |  | [21]      |
|          |                           |   | MT-2                   | EC50<br>246.7 nM;<br>4 h                       |  |  |           |
| In vitro | Methyl angolensate        | <i>Soyimida febrifuga</i>                     | Daudi                  | 10, 50,<br>100, 250<br>µM; 24, 48,<br>72 h     | Inhibition of proliferation<br>Activation of apoptosis<br>ROS formation  | ↑ c-PARP,<br>MRE11,<br>RAD50,<br>NBS1, p-ATM,<br>KU70, KU80<br>↓ p53, p73  | [22]      |
|          | Oxypeucedanin             | <i>Ducrosia anethifolia</i>                   | L5178Y PAR             | IC50 25.98<br>µM                               | Inhibition of proliferation  |  |           |
|          |                           |   | L5178Y MDR             | IC50 28.89<br>µM                               |  |  |           |
| In vitro | Oxypeucedanin methanolate | <i>Ducrosia anethifolia</i>                   | L5178Y MDR             | IC50 35.88<br>µM                               | Inhibition of proliferation  |  | [20]      |
|          |                           |   | L5178Y PAR             | IC50 33.23<br>µM                               |  |  |           |
|          | Pabulenol                 | <i>Ducrosia anethifolia</i>                   | L5178Y MDR             | IC50 30.47<br>µM                               | Inhibition of proliferation  |  |           |
|          |                           |   | L5178Y PAR             | IC50 29.28<br>µM                               |  |  |           |
| In vitro | Peperobtusin A            | <i>Peperomia tetraphylla</i>                  | U937                   | 25, 50, 75,<br>100 µM; 1,<br>3, 6, 24          | Induction of cell cycle arrest and apoptosis   | ↑ ROS, Bax,<br>c-caspase-8,<br>-9, -3, p-p38<br>↓ MMP, Bcl-2,<br>Bid, caspase-3, p38   | [24]      |
| In vitro | Psilostachyin C           | <i>Ambrosia</i> spp.                          | BW5147                 | 10 µg/mL;<br>24 h                              | Induction of apoptosis, necrosis<br>Cell arrest in S phase<br>Inhibition of cell viability, cell proliferation | ↓ SOD, CAT,<br>Px  | [25]      |
| In vitro | Resveratrol               | Various plants                                | Ramos                  | 20, 50, 70,<br>100 µM; 1,<br>3, 6, 10, 24<br>h | Induction of antiproliferative and proapoptotic activity   | ↑ c-caspase-3, c-PARP,<br>NOXA,<br>PUMA, p-ATM, p-BRCA1, γ-H2AX, Rad50, Mre 11, p-p95, DNA-PKcs, KU80<br>↓ TCL-1. Myc, Bach2 | [26]      |
|          |                           |   |                        |  | Induction of cell cycle arrest   | ↓ Cyclin A2  |           |
| In vitro | Resveratrol               | Various plants                                | SNT-8, SNK-10, SNT-16  | 25 µM; 0.5,<br>1, 3, 6, 12,<br>24, 48 h        | Induction of DNA damage response and apoptosis<br>Inhibition of proliferation                                  | ↑ pATM, γ-H2A.X., p-Chk2, p-p53, Bax, Bad, c-caspase-9, -3<br>↓ Mcl-1, survivin, p-AKT, p-Stat3                              | [27]      |

| System   | Compound                             | Source                                     | Cell Line/Animal Model  | Dose; Duration                           | Efficacy   | Mechanism   | Reference |
|----------|--------------------------------------|--|-------------------------|--|--|---|-----------|
| In vitro | Rotenone                             | <i>Amorpha fruticosa</i>                   | L5178Y                  | IC50 0.3 $\mu$ M                         | Induction of cytotoxicity  |   | [17]      |
|          | rot-2'-enonic acid                   | <i>Amorpha fruticosa</i>                   | L5178Y                  | IC50 0.6 $\mu$ M                         | Induction of cytotoxicity  |   | [17]      |
| In vitro | Schweinfurthin                       | <i>Macaranga alnifolia</i> Baker           | WSU-DLCL2               | 100 nM; 24 h                             | Inhibition of proliferation                                      | $\uparrow$ p-EIF2a<br>$\downarrow$ mTOR, AKT  | [28]      |
| In vitro | Sermundone                           | <i>Amorpha fruticosa</i>                   | L5178Y                  | IC50 0.2 $\mu$ M                         | Induction of cytotoxicity  |   | [17]      |
|          |                                      |  | BC-1                    |  | Induction of apoptosis<br>Increase ROS generation<br>Loss of MMP | $\uparrow$ Bax, c-caspase-3, -9, c-PARP, DR5<br>$\downarrow$ Bcl-2, p-AKT, p-FOXO1, p-GSK3, p-Bad   |           |
| In vitro | Thymoquinone                         | <i>Nigella sativa</i>                      | BC-3                    | 10, 25 $\mu$ M; 24 h                     | Induction of apoptosis, ROS generation                           | $\uparrow$ Bax, c-caspase-3, -9, c-PARP<br>$\downarrow$ Bcl-2, p-AKT, p-FOXO1, p-GSK3, p-Bad  | [30]      |
|          |                                      |  | BCBL-1                  |  | Induction of apoptosis, ROS generation                           | $\downarrow$ p-AKT, p-FOXO1, p-GSK3, p-Bad  |           |
|          |                                      |  | HBL-6                   |  | Induction of apoptosis   |   |           |
| In vitro | Thymoquinone                         | <i>Nigella sativa</i> Linn.                | ABC-DLBCL (HBL-1, RIVA) | 5, 10 mM; 24 h                           | Induction of ROS and apoptosis<br>Inhibition of cell viability   | $\uparrow$ c-caspase-9, -3, PARP, Bax<br>$\downarrow$ NF- $\kappa$ B, I $\kappa$ Ba, Bcl-2, Bcl-Xl, XIAP, Survivin, translocation of p65 subunit of NF- $\kappa$ B, p-p65 | [29]      |
| In vitro | Tylophorine N-oxide                  | <i>Citrus tachibana</i> (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                | <i>Citrus tachibana</i> (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-hydroxyisotylcrebrine | <i>Citrus tachibana</i> (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-methylelagic acid     | <i>Combretum dolichopetalum</i>            | L5179Y                  | IC50 29.0 $\mu$ M                        | Induction of cytotoxicity  |   | [15]      |
| In vitro | 4-Deoxyraputindole C                 | <i>Raputia praetermissa</i>                | Raji                    | 20, 40, 60, 80, 100 $\mu$ M; 6, 12, 24 h | Induction of cell death  | $\uparrow$ mitochondrial superoxide<br>$\downarrow$ MMP, cathepsin B/L  | [31]      |

| System               | Compound                                  | Source  | Cell Line/Animal Model | Dose; Duration              | Efficacy  | Mechanism   | Reference |
|----------------------|---|---|------------------------|-----------------------------|---|---|-----------|
| In vitro             | 6a,12a- dehydrodeguelin                   | <i>Amorpha fruticosa</i>                      | L5178Y                 | IC50 10.2 $\mu$ M           | Induction of cytotoxicity   |   | [17]      |
| In vitro             | 6'-O- $\beta$ -D-Glucopyranosyldalpanol   | <i>Amorpha fruticosa</i>                      | L5178Y                 | IC50 1.7 $\mu$ M            | Induction of cytotoxicity   |   | [17]      |
| In vitro             | 14-hydroxytylophorine N-oxide             | <i>Citrus tachibana</i> (Makino)<br>T. Tanaka | MT-1                   | EC50 69.8 nM; 4 h           | Inhibition of proliferation   |   | [22]      |
| In vitro             | $\alpha$ -toxicarol                       | <i>Amorpha fruticosa</i>                      | L5178Y                 | IC50 0.2 $\mu$ M            | Induction of cytotoxicity   |   | [17]      |
| In vitro             | $\beta$ -Asarone                          |   | Raji                   | 100, 200, 400 $\mu$ M; 72 h | Induction of apoptosis  | $\uparrow$ c-caspase-9, -3, c-PARP<br>$\downarrow$ procaspase-9, -3, PARP | [32]      |
| In vitro             | $\beta$ -Phenethyl isothiocyanate (PEITC) |   | Raji                   | 10 $\mu$ M; 3 h             | Reduction in mitochondrial respiration rate<br>Increase in cellular H <sub>2</sub> O <sub>2</sub> levels<br>Rapid depletion of cellular and mitochondrial glutathione | $\downarrow$ NDUFS3   | [33]      |
| In vitro             | (b)-Oxypeucedanin hydrate                 | <i>Ducrosia anethifolia</i>                   | L5178Y MDR             | IC50 41.96 $\mu$ M          | Inhibition of proliferation   |   | [21]      |
|                      |   |   | L5178Y PAR             | IC50 60.58 $\mu$ M          |   |   |           |
|                      | Compound 6                                |   | L5178Y                 | IC50 11.38 $\mu$ M; 24 h    |   |   |           |
|                      | Compound 8                                |   | L5178Y                 | IC50 63.91 $\mu$ M; 24 h    |   |   |           |
|                      | Compound 9                                |   | L5178Y                 | IC50 35.56 $\mu$ M; 24 h    |   |   |           |
| In vitro             | Compound 10                               | <i>Tabernaemontana elegans</i> Stapf          | L5178Y                 | IC50 29.21 $\mu$ M; 24 h    | Induction of cytotoxicity   |   | [34]      |
|                      | Compound 15                               |   | L5178Y                 | IC50 34.28 $\mu$ M; 24 h    |   |   |           |
|                      | Compound 16                               |   | L5178Y                 | IC50 20.77 $\mu$ M; 24 h    |   |   |           |
|                      | Compound 23                               |   | L5178Y                 | IC50 33.30 $\mu$ M; 24 h    |   |   |           |
| In vitro and in vivo | Chelerythrine                             | <i>Chelidonium majus</i> . L.                 | BALB/c (H2d) mice      | 1.25, 2.5 mg/kg; 34 d       | Increase in survival duration<br>Inhibition of Dalton's Lymphoma cell growth  |   | [35]      |
|                      |   |   | TANK                   | 2.5 mg/kg                   |   | $\uparrow$ NKG2D<br>$\downarrow$ NKG2A                                    |           |

| System               | Compound                     | Source                               | Cell Line/Animal Model                   | Dose; Duration                           | Efficacy   | Mechanism  | Reference |
|----------------------|------------------------------|--------------------------------------|--|--|--|--|-----------|
| In vitro and in vivo | Elatol                       |                                      | SU-DHL-6, OCI-Ly3, RIVA                  | 500 nM, 1, 10 $\mu$ M; 24, 48, 72, 96 h  | Induction of apoptosis                                   |  | [36]      |
|                      |                              |                                      | SU-DHL-6, OCI-Ly3                        | 5 $\mu$ M; 16 h                          |  | $\downarrow$ cyclinD3, MYC, MCL1, PIM2   |           |
|                      |                              |                                      |  | 1, 10 $\mu$ M; 4, 16, 24 h               | Inhibition of protein synthesis                          |  |           |
|                      |                              |                                      | OCI-Ly3                                  | 5 $\mu$ M; 16 h                          |  | $\downarrow$ BCL-2, survivin   |           |
|                      |                              |                                      | SCID mice(engrafted with SU-DHL-6)       | 20 mg/kg; 20 days                        | Inhibition of tumor growth                               |  |           |
|                      | SCID mice(OCI-Ly3 xenograft) | 40 mg/kg; 30 days <sup>†</sup>       |  |  |  |  |           |
| In vitro and in vivo | Fucoxanthin                  | <i>Cladosiphon okamuranus</i> Tokida | BCBL-1                                   | 2.5, 5, 10 $\mu$ M; 24 h                 | Induction of apoptosis                                   | $\uparrow$ c-PARP, c-caspase-3, -8, -9   | [37]      |
|                      |                              |                                      | BCBL-1                                   | 2.5, 5, 10 $\mu$ M; 24 h                 | Induction of cell cycle arrest                           | $\downarrow$ Bcl-xL, XIAP, p-pRb p-IKK $\beta$ , p-IkB $\alpha$ , IKK $\alpha$ , IKK $\beta$ , IKK $\gamma$ , Akt, PDK1, p-caspase-9, $\beta$ -catenin, JunB, JunD |           |
| In vitro and in vivo | Pterostilbene                |                                      | SCID mice (BCBL-1 Xenograft)             | 150 mg/kg; 56 days                       | Inhibition of tumor growth                               |  | [38]      |
|                      |                              |                                      | Jeko-1, Granta-519, Mino, Z-138          | 10, 20, 40, 60, 80 $\mu$ M; 24, 48, 72 h | Induction of cytotoxicity                                | $\uparrow$ c-caspase-3, -8, -9, Bax<br>$\downarrow$ CDK4, CDK6,  |           |
|                      |                              |                                      | Jeko-1, Granta-519                       | 20, 40, 80 $\mu$ M; 48 h                 | Induction of cell cycle arrest and apoptosis             | cyclinD1, MMP, Bcl-2, Bcl-xL, p-PI3K, p-Akt, p-mTOR, p-p70S6K  |           |
| In vitro and in vivo | Resveratrol                  | Various plants                       | NOD/SCID mice (JeKo-1 Xenograft)         | 50 mg/kg; 15 days                        | Inhibition of tumor growth                               | $\downarrow$ p-mTOR  | [39]      |
|                      |                              |                                      | EL4                                      | 5, 10, 25, 50, 100 $\mu$ M; 6, 12, 24 h  | Induction of apoptosis                                   | $\uparrow$ AhR, Fas, FasL, Sirt1, Bax, Bid, cytochrome-c, SIRT1<br>c-caspase-8, -3, -9, c-PARP<br>$\downarrow$ p-IkB $\alpha$ , NF- $\kappa$ B                     |           |
| In vitro and in vivo | Resveratrol                  | Various plants                       | NOD/SCID/<br>yc <sup>null</sup> mice/EL4 | 10, 50, 100 mg/kg; 38 days               | Suppression of tumor growth<br>Increase in survival time |  | [39]      |
|                      |                              |                                      |  |  |  |  |           |

| System                                | Compound                | Source                     | Cell Line/Animal Model                        | Dose; Duration         | Efficacy   | Mechanism                                    | Reference |
|---------------------------------------|-------------------------|----------------------------|---|------------------------|--|--|-----------|
| In vitro and in vivo                  | 11(13)-dehydroivaxillin | <i>Carpesium genus</i>     | Daudi, Namalwa, SU-DHL-4, SU-DHL-2            | 5, 7, 10 $\mu$ M; 24 h | Induction of apoptosis   | $\uparrow$ c-PARP, c-caspase-3               | [40]      |
|                                       |                         |                            | SU-DHL-2, NAMALWA                             |                        |  |  |           |
|                                       |                         |                            | Daudi, NAMALWA, SU-DHL-2                      | 5, 10 $\mu$ M; 6 h     | $\downarrow$ cyclin D1, Bcl-2, I $\kappa$ B $\alpha$ ,                   |  |           |
|                                       |                         |                            |   | 10 $\mu$ M; 4 h        |  | $\downarrow$ p-I $\kappa$ B $\alpha$ , p-p65 |           |
|                                       |                         |                            | Daudi, SU-DHL-2                               | 5, 7 $\mu$ M; 24 h     | $\downarrow$ IKK $\alpha$ /IKK $\beta$ , c-MYC, cyclinD1, NF- $\kappa$ B |  |           |
| B-NSG mice(Daudi, SU-DHL-2 xenograft) | 50 mg/kg; 10 days       | Inhibition of tumor growth | $\downarrow$ IKK $\alpha$ /IKK $\beta$ , PCNA |                        |  |  |           |

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); I $\kappa$ B kinase (IKK); phosphoinositide dependent protein kinase (PDK); nuclear factor kappa B (NF $\kappa$ B); activator protein (AP); cellular inhibitor of apoptosis protein (cIAP); forkhead box protein O1 (FOXO1); glycogen synthase kinase (GSK); proliferating cell nuclear antigen (PCNA); glucose-regulated protein (GRP); CCAAT/enhancer-binding protein homologous protein (CHOP); 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).

### 3. Animal-Derived Compounds and Lymphoma

Some animal-derived compounds were reported to have anticancer efficacies against lymphoma (Table 3). Annomontine, ingenines A, and B are alkaloids obtained from the methanol extract of *Acanthostrongylophora ingens*, the Indonesian sponge [41]. Annomontine and ingenines B exerted cytotoxicity against L5178Y cells with the ED50 values 7.8 and 9.1  $\mu$ g/mL, respectively. However, ingenines A showed little cytotoxic properties. Mokhlesi et al. demonstrated that isolated compounds from Indonesian marine sponge of the genus *Cinachyrella* exerted cytotoxicity against L5178Y mouse lymphoma cells [42]. This sponge is known for its therapeutic effects to produce steroids and fatty acid metabolisms. Cinachylenic acids A, B, C, and D were acetylenic acid derivatives exhibiting pronounced cytotoxicity with an IC50 value of 0.3  $\mu$ M. Cinobufotalin is a kind of bufadienolide which originates from the venom of the skin secretions of giant toads such as *Bufo gargarizans* [43]. Cell viability and MMP declined in the U937 cells treated with cinobufotalin (0.5 and 1  $\mu$ M for 6, 12 and 24 h). Rapid release of cytosolic superoxide anion and increase in intracellular Ca<sup>2+</sup> were also observed. Expressions of Fas and caspase-3 and caspase-8 cleavage were elevated, whereas procaspase-2, -3, -8, -9, cytosolic Bid, and Bax protein levels declined. These findings suggest that cinobufotalin induces apoptosis via both the intrinsic and extrinsic pathways. Dyshlovoy et al. reported that frondoside A (FrA), a natural compound extracted from sea cucumber *Cucumaria okhotensis*, exerted caspase-3/p53-independent apoptosis and inhibited prosurvival autophagy in BL cells [44]. After FrA treatment, cell cycle arrest at the G1 phase was observed in CA46, Namalwa, Ramos, and BL-2. Cleavage of PARP and decreased survivin and Bcl-2, which are known as antiapoptotic proteins, were observed in CA46. It was also confirmed that FrA induced translocation of mitochondrial proteins, including cyt C, apoptosis inducing factor (AIF), and HtrA1/Omi, from mitochondria to cytosol in CA46, BL-2, and Ramos. In addition, accumulation of LC3B-I/II and sequestosome (SQSTM) 1/p62 known to be associated with autophagy was verified. Iodocionin is a compound isolated from the mediterranean ascidian *Ciona edwardsii* by A. Aiello et al. [45]. L5178Y mouse lymphoma cell lines treated with 0.1, 0.3, 1, 3, 10  $\mu$ g/mL idiocionin formula for 72 h displayed lower levels of cell viability. The brominated analogue of idiocionin, its iodine transferred into bromine, featured similar bioactivity against L5178Y cells. Ebada et al. reported that compounds isolated from marine sponge *Jaspis splendens* such as (+)-jasplakinolide Z6, (+)-jasplakinolide, (+)-jasplakinolide Z5, and (+)-jasplakinolide V exhibited cytotoxicity against L5178Y [46]. The IC50 value of (+)-jasplakinolide

Z6 was 3.2  $\mu$ M, and the rest was less than 100 nM. Interestingly, frondoside A(frA), extracted from sea cucumber *Cucumaria okhotensis*, changed not only autophagy relating 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. Marine 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  | <i>Acanthostrongylophoraingens</i> | L5178Y                     | ED50 7.8 $\mu$ g/mL                 | Induction of cytotoxicity   |   | [41]      |
| Cinachylenic Acid A, B, C, D                                       | <i>Cinachyrella</i> sp.            | L5178Y                     | IC50 0.3 $\mu$ M                    | Induction of cytotoxicity   |   | [42]      |
| Cinobufotalin  | Toad                               | U937                       | 0.5, 1 $\mu$ M; 6, 12, 24 h         | Decrease in cell viability and MMP Rapid release of cytosolic superoxide anion, increase in intracellular $[Ca^{2+}]$ | $\uparrow$ Fas, c-caspase-3, -8<br>$\downarrow$ Pro-caspase-2, -3, -8, -9, cytosolic Bid, cytosolic Bax | [43]      |
| Frondoside A   | <i>Cucumaria frondosa</i>          | CA46, Namalwa, Ramos, BL-2 | 0.3, 0.6 $\mu$ M; 48 h              | Induction of cell cycle arrest  |   |           |
|  |                                    | CA46                       | 0.3 $\mu$ M; 48 h                   | Inhibition of prosurvival autophagy   | $\uparrow$ LC3B-I/II, SQSTM1/p62  | [44]      |
|  |                                    | CA46, BL-2, Ramos          | 0.3, 0.6 $\mu$ M; 48 h              | Induction of apoptosis  | $\uparrow$ c-PARP<br>$\downarrow$ Survivin, Bcl-2   |           |
| Ingenine B   | <i>Acanthostrongylophoraingens</i> | L5178Y                     | ED50 9.1 $\mu$ g/mL                 | Induction of cytotoxicity   |   | [41]      |
| Iodocionin   | <i>Ciona edwardsii</i>             | L5178Y                     | 0.1, 0.3, 1, 3, 10 $\mu$ g/mL; 72 h | Inhibition of cell proliferation  |   | [45]      |
| (+)-Jasplakinolide.<br>(+)-Jasplakinolide Z5, (+)-Jasplakinolide V | <i>Jaspis splendens</i>            | L5178Y                     | IC50 < 100 nM                       | Induction of cytotoxicity   |   | [46]      |
| (+)-Jasplakinolide Z6  |                                    |                            | IC50 3.2 $\mu$ M                    |   |   |           |

Cleaved poly ADP ribose polymerase (c-PARP); sequestosome (SQSTM); cytochrome C (Cyt C); apoptosis inducing factor (AIF).

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