Leukemia Research 104 (2021) 106554

Contents lists available at ScienceDirect

Leukemia Research

journal homepage: www.elsevier.com/locate/leukres

Treatment of lymphomas via regulating the Signal transduction pathways by natural therapeutic approaches: A review

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ARTICLE INFO

Keywords:
Lymphoma
Natural products
Risk factors
Anti-cancer agents
Resveratrol
Apoptosis
Cell-proliferation
Bromelain
MK615
EGCG

ABSTRACT

Lymphoma is a heterogeneous group of malignancies, which comprises 4.2 % of all new cancer cases and 3.3 % of all cancer deaths in 2019, globally. The dysregulation of immune system, certain bacterial or viral infections, autoimmune diseases, and immune suppression are associated with a high risk of lymphoma. Although several conventional strategies have improved during the past few decades, but their detrimental impacts remain an obstacle to be resolved. However, natural compounds are considered a good option in the treatment of lymphomas because of their easy accessibility, specific mode of action, high biodegradability, and cost-effectiveness. Vegetables, fruits, and beverages are the primary sources of natural active compounds. The present review investigated the activities of different natural medicinal compounds including curcumin, MK615, resveratrol, bromelain, EGCG, and *Annonaceous acetogenins* to treat lymphomas. Moreover, *in vitro* and *in vivo* studies, classification, risk factors, and diagnosis of lymphoma are also discussed in the present review. The accumulated data proposed that natural compounds regulate the signaling pathways at the level of cell proliferation, apoptosis, and cell cycle to exhibit anti-lymphoma activities both *in-vivo* and *in-vitro* studies and suggested that these active compounds could be a good therapeutic option in the treatment of different types of lymphomas.

1. Introduction

Lymphomas are known as a heterogeneous group of malignancies, with multiple sets of causes, natural progression and comprise more than 3 % of all malignancies [1,2]. It is a cancer of the lymphatic system, which acts as a filter of the body consist of lymph nodes and a web of vessels [3]. All lymphoid malignancies originate from systemic lymphoid tissues and can spread over the other parts of the body [4]. According to accumulated data, approximately 85–90 % of lymphomas are derived from B lymphocyte cells, whereas remaining originate from T lymphocyte cells and natural killer cells [5]. Lymphomas are majorly classified into two main classes including Non- Hodgkin lymphoma (NHL) (accounts 90 % of lymphomas) and Hodgkin's lymphoma (HL) (accounts for only 10 % of all lymphomas) [5]. Lymphoid malignancies are presented with highly diverse features including enlarged lymph nodes and systemic symptoms of fatigue, fever, weight loss, and extra lymphatic spread are also seen initially in patients who are suffering from both HL and NHL [6,7].

According to the emerging evidence, the NHL is ranked as the 7th most general cancer among men and 6th most commonly diagnosed cancer among women [8]. Globally, approximately 510,000 new confirmed cases of NHL were estimated in 2018, and wildly it is ranked as the 5th - 9th most common cancer in most of the countries [9]. The incidences and deaths due to NHL across the globe vary with different geographical regions [10]. In most of the Middle East countries, the relative frequency of NHL seems to be lower than HL in contrast with the

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https://doi.org/10.1016/j.leukres.2021.106554
Received 1 February 2021; Received in revised form 25 February 2021; Accepted 26 February 2021
Available online 2 March 2021

global burden of diseases. A study reported that the incidence rate of NHL was higher among developing countries including Pakistan, India, Sudan, and Bangladesh which comprise about 50.5 % of the world cases. Globally, a 2.4 % death rate was estimated due to NHL and two-third of them (125,000) deaths were occurring in underdeveloped countries due to poor survival in these regions [11]. The emerging evidence suggested that the Burkitt lymphoma (BL), diffuse large B cell lymphoma, anaplastic lymphoma and lymphoblastic lymphoma (LL) are major types identified in children mostly [12]. The incidence rate of NHL was higher specifically Burkitt lymphoma and HL which comprises 6 and 3% respectively in children, whereas HL accounts for 13 % of adolescent cancers (aged 15–19 years) [13].

According to emerging evidence, the dysregulation of the immune system is considered as one of the high-risk factors for lymphoma [14]. The autoimmune disordered is also associated with the best-established risk factor for lymphomas. In addition, the few medications (tumor necrosis inhibitors) during the treatment of autoimmune disordered are also associated with a high risk of Hodgkin and non-Hodgkin Lymphomas [15]. Younes and co-workers revealed that the occurrence of lymphomas also associated with a bacterial and viral infection like Epstein-Barr virus caused the risk of high-grade B-cell, primary effusion, and Burkitt lymphomas [16]. However, the diagnosis is a necessary and important thing before the treatment of distinct types of lymphomas. For diagnostic evaluation, the determination of tissue is required to check the presence of lymphoma for the treatment plan [17]. Needle core biopsy is increasingly used for lymphadenopathy malignancy diagnosis, it not only provides a definite diagnosis but also helped in the differentiation of multiple lymphomas [18]. In addition to biopsy, biomarkers including an elevated level of serum cytokines [19] and lactate dehydrogenase (LDH) are also used for the diagnosis of lymphomas [20].

According to accumulated data, different therapies including chemotherapy (dacarbazine, bleomycin, or doxorubicin) and radiotherapy are considered as standard single or combined treatment modalities against lymphomas [16]. A recently published study reported that in addition to the positive effects of these therapies, they also exert a number of adverse effects on different body organs including skin, reproductive, cardiovascular, renal, hematological, and neurological systems [21]. Human epidemiological studies showed that the consumption of natural products is considered a promising therapy against different cancers including lymphomas due to their less adverse effects, specificity, high biodegradability, easy accessibility, and greater mode of action [22–24]. The *in-vivo* and *in-vitro* studies reported that the medicinal plants (*Glycine max*, *Ananas Comosus*, *Vitis vinifera*, *Prunus mume*, Curcuma longa, *Momordica charantia*, and *Zingiber Officinalis*) modulate different signal pathways including apoptosis, inhibition of cell proliferation, cell cycle arrest at (G1/S phase), deactivation/activation of NF-κB pathway, regulation of signaling caspases, up-regulation of antioxidant enzymes, epigenetic modulation, metastasis, and inhibition of PI3K/Akt/mTOR pathway in the treatment of lymphomas [14, 25–29]. Shanmugam et al. [30] reported that curcumin (natural compound) induced apoptosis and cell-cycle arrest (G1/S) in the treatment of Hodgkin lymphoma. Similarly, 25–300 μM administration of resveratrol effectively regulates the death receptor pathway by activation of EBV lytic antigens during the treatment of Raji/Akata cell lines of lymphocytes [31].

However, according to the epidemiology of lymphoma, there is a need to develop a strong therapeutic drug with unique characteristics and less adverse effects to control the mortality rate. To handle this situation, despite research manuscripts, the review article has equal importance to highlight and recommend the solutions. The present review investigates the anti-lymphomas activities of Curcuma longa, *Prunus mume*, *Vaccinium macrocarpon* (resveratrol), *Ananas comosus*, *Camellia sinensis,* and *Annona muricata*. Moreover, the classification, risk factors, and diagnosis of lymphomas are also discussed in the present review for a better understanding.

Table 1
The classification of Hodgkin and non-Hodgkin lymphoma.

Main class	Subclass	Percentage (%)	Reference
Hodgkin's Lymphoma	Nodular sclerosis classical Hodgkin's lymphoma (NSCHL)	60–75	[38,112]
	Mixed cellularity classical Hodgkin's lymphoma (MCCHL)	20–25	[38,112]
	Lymphocyte-depleted classical Hodgkin's lymphoma (LDCHL)	less than 1	[38,112]
	Lymphocyte-rich classical Hodgkin's lymphoma (LRCHL)	5 with LRCHL	[38,112]
	Nodular Lymphocyte-predominant HL (NLPHL)	5	[112, 113]
Non-Hodgkin's Lymphomas	Diffused large B- cell lymphoma (DLBCL)	32.5	[114]
	Follicular Lymphoma (FL)	17.1	[114]
	Marginal Zone lymphoma (MZL)	8.3	[114, 115]
	Mantle-cell lymphoma (MCL)	3–10	[116]
	Peripheral T-cell lymphoma (not otherwise specified – PTCL (NOS))	1.7	[114]
	Burkitt lymphoma (BL)	1.6–2.2	[1,115]
	Anaplastic large cell lymphoma (ALCL)	1	[114]
	Extranodal NK/T-cell lymphoma (ENKL)	2.2	[115]
	Mucosa-associated lymphoid-tissue (MALT) lymphoma	5	[117]
	Lymphoplasmacytic lymphoma (LPL)	1.1	[114, 118]
	Others	18.9	[114]

2. Classification of lymphoma

Lymphomas are classified into two main classes including rare Hodgkin and common non- Hodgkin lymphoma [32]. Nodular lymphocyte-predominant Hodgkin lymphoma (LPHL) is a relatively uncommon HL that comprises 5–10 % of all Hodgkin lymphomas and shows unique clinicopathological features (cervical region and axillary region) compared to classical HL [33]. Classical HL account for about 85 % of all HL cases [33]. Nodular sclerosis classical HL (NSCHL) [34], mixed cellularity HL [35], lymphocyte-depleted HL (LDCHL) [36] and lymphocyte- rich classical Hodgkin's lymphoma (LRCHL) are further subgroups of classical Hodgkin's lymphoma [37,38], as presented in Table 1. NSCHL exhibits major differences from lymphocyte-depleted (LD) and mixed cellularity (MC) HL, so these are recognized as separate entities [33]. More common lymphoma which occurred all over the world is NHL, there are many subtypes of NHL as presented in Table 1. DLBCL is the most common subclass of NHL in elderly people [39], and FL is considered as the second most common subtype of NHL in the Western population [40]. According to accumulated data, yet more than 50 various subtypes of T and B-cell NHL had been defined, each subtype has unique clinic-pathological and biological characteristic [41].

3. Risk factors for lymphoma

Cancer incidences and deaths vary in different geographical regions because of unequal distribution of risk factors for cancer [10]. Regarding the entity of risk factors of lymphoma, extensive investigation is done to govern how and whether lymphomas are associated with prior medical conditions, fitness records, or other conditions including blood transfusions, smoking, or use of other carcinogens. Few risk factors of lymphomas are presented in the following sections.

3.1. Genetics

Cytokines are small signaling proteins that are produced and released primarily by cells of innate and adaptive immunity, but also by

epithelial and stromal cells and help in the regulation of immune responses to external stimuli (temperature, heat, environmental factors) [42,43]. Cytokine proteins play an important role in immune regulation [44]. The key function of cytokines is to regulate the inflammatory response. The disturbed balance between immune response and anti-tumor activity leads to cancer development [44]. Nuclear factor-kappa B (NF-κB) and JAK/STAT pathways are reported as the signaling pathways for cytokines' receptors [45,46]. Tumor burden in patients is reflected by serum specific cytokine profiles. The soluble mediators' cytokines are produced by reactive cells or tumor cells which can contribute to tumor development [47]. Tumor necrosis factor (TNF) and Interleukin 10 (IL10) are the genes that code for some immune-regulatory cytokines which are associated with serious mediators of programmed cell death, inflammation and T-cell subsets (Type 1 T-helper cell and Type 2 T-helper cell balance), and function as autocrine growth factors (HB-EGF and Amphiregulin) in lymphoma [48–50].

3.2. Polymorphism in xenobiotic metabolizing enzyme

Polymorphism in genes that encoded xenobiotic metabolism enzymes (N-acetyltransferases and glutathione S-transferase) increased the susceptibility of developing lymphomagenesis [51,52]. A study suggested that the people who mostly use hair dyes are at higher risk of NHL, especially females. Chemicals present in hair dyes cause polymorphisms that disturbed the enzymic activity and its normal functioning [53].

3.3. Acquired and autoimmune situations

Certain acquired and autoimmune situations, hypersensitive reactions, and inflammatory diseases such as primary Sjogren's syndrome (pSS), rheumatoid arthritis, and systemic lupus erythematosus (SLE), are considered as high-risk factors for lymphoma [5,16,54]. Several studies conducted in different patients showed that the high incidences of lymphoma are mainly associated with an autoimmune condition. But the relationship between lymphoma and autoimmune condition remains unclear [55]. Kaulen et al. [56] reported that the administration of immunosuppressive agents (azathioprine, cyclosporine, leflunomide, and chlorambucil) for autoimmune diseases (AID) and solid organ transplantations (SOT) are also considered as a high-risk factor for NHL.

3.4. Bacterial and viral infections

Among various types of cancers, lymphoma malignancies are first discovered that are associated with infectious agents cause by either bacteria or viruses including Human T-lymphotropic virus-1(HTLV-1), and Epstein–Barr virus (EBV) particularly caused Burkitt lymphoma and high-grade B-cell lymphoma [16]. According to emerging evidence, the hepatitis B virus infection is also found to be associated with lymphoma malignancies. The patient who suffered from hepatitis B virus infection has a higher risk of B-cells (diffused large B cell lymphoma; DLBCL) [57]. *Helicobacter Pylori* (HP) was the first bacteria that was recognized to play a causative role in the development of human malignancies including lymphoma [58]. Evidence showed that bacterial infections caused Mucosa-associated lymphoid tissue Lymphoma (gastric MALT lymphoma) in humans [59,60].

4. Diagnosis

Lymphoma has extensively varying genetic abnormalities, immunophenotyping and clinical features [61]. Patients with lymphoma might suffer from ambiguous symptoms such as weight loss, and low-grade fever, or altered hematological laboratory values. The biopsy technique was considered as the most promising technique for the initial diagnosis of lymphoma [32]. The utilization of biopsy not only allows diagnosis but also helps to identify the subclassification of lymphoma.

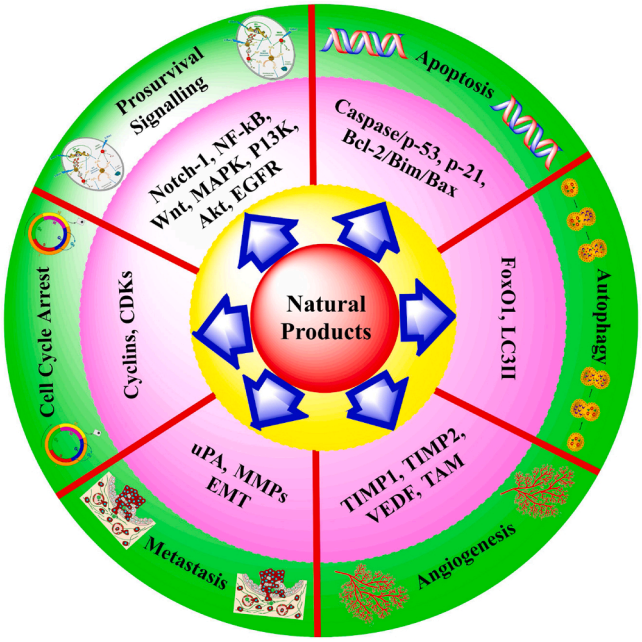


Fig. 1. The anti-cancerous activities of natural compounds by regulating different pathways.

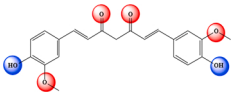
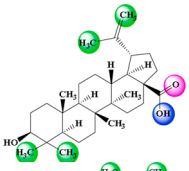
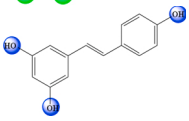
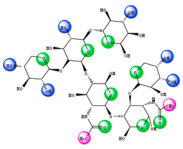
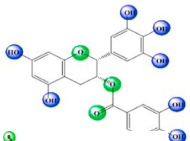
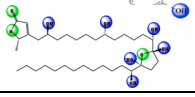
Recently needle-core biopsy for the lymphoma diagnosis has proven as less adverse traumatic, properly tolerated, and cost-effective mainly for the patients who have deep-seated lesions or poor clinical situations [62]. A study also suggested that ultrasound-guided full core needle biopsy (UFCNB) offers the best alternatives for the diagnosis of lymphoma with a 95.0 % accuracy rate, and 97.2 and 88.7 % sensitivity for NHL and HL, respectively [63].

The other biochemical parameters are also used for lymphoma diagnosis. The cytokine estimation by enzyme-linked immunosorbent assays helped in the assessment of lymphoma patients at clinical and laboratory levels [64]. Besides, non-specific tumor marker namely lactate dehydrogenase (LDH) raised in the case of lymphoma [20]. Serum levels of lactate dehydrogenase are determined to diagnose lymphoma. Enzyme lactate dehydrogenase-5 catalysis the formation of lactate from pyruvate in the presence of NAD^+ at the end of the glycolysis process. The up-regulation of this process is found in several malignant tumors including lymphomas [65].

5. Medicinal plants for the treatment of lymphoma

For most lymphomas, the natural products (curcumin, MK615, resveratrol, and bromelain) are considered as a standard treatment due to their accurate mode of action, greater bioavailability, specificity, cost-effectiveness, and fewer adverse effects [21,27]. Human epidemiological statistics showed a greater connection between diets rich in vegetables, and fruits, and reduction of cardiac diseases and cancers [66]. Polyphenols are considered as potent anticancer agents, they exert their anticancer activity through a wide range of processes including they inhibit one or more biochemical pathways and biomolecules that help in the treatment of cancer cells [67,68]. One of the possible strategies for the treatment of lymphomagenesis is to target signaling pathway of NF-κB by natural approaches that regulate the expression of thousands of genes [69]. Besides, natural compounds induce apoptosis, angiogenesis, metastatic, autophagy, cell-proliferation, and cell cycle arrest to treat the cancer cells including lymphoma (see Fig. 1) [27]. Following different medicinal plants are discussed to reduce and control the epidemiology of lymphoma.

Table 2
The representative structures of natural compounds with their sources and molecular mass.

Plant	Active compound	Molecular formula	Chemical Structure	Identification ID	Reference
Curcuma longa (Turmeric)	Curcumin	$C_{21}H_{20}O_6$		969,516	[119]
	Ursolic acid	$C_{30}H_{48}O_3$		64,945	[120]
Prunus mume (Japanese apricot)	Betulinic acid	$C_{30}H_{48}O_3$		64,971	[121]
	Oleanolic acid	$C_{30}H_{48}O_3$		10,494	[122]
Vitis vinifera (Grape vine)	Resveratrol	$C_{14}H_{12}O_3$		445,154	[123]
Ananas comosus (Pineapple)	Bromelain	$C_{39}H_{66}N_2O_{29}$		44,263,865	[124]
Camellia sinensis (Green tea)	EGCG	$C_{22}H_{18}O_{11}$		65,064	[125]
Annona muricata (Annona fruits)	*Annonaceous acetogenins*	$C_{26}H46O7$		393,472	[126]

5.1. Curcumin

Curcumin (diferuloylmethane) is a natural product of yellow-colored Phyto-polyphenol derived from Curcuma longa herb root (see Table 2). During the past couple of decades, curcumin extensively studied as an anti-cancerous agent against multiple myeloma including lymphomas by suppressing cell-proliferation, cellular transformation, invasion, metastasis, and angiogenesis [70,71]. Mackenzie and his research group reported that curcumin plays a significant role in the reduction/control of lymphomas of about 80.97 % by suppressing the activation of NF-kB and STAT-3 factors, cell cycle arrest, inhibit the expression of cell-proliferated proteins and apoptosis [72]. Similarly, *in vivo* study demonstrated that the nano-scaled TPGS-curcumin and SLN-curcumin effectively reduced the lymphoma (HL) effect in mice by 43 % ($p < 0.04$) and 50.5 % ($p < 0.02$) respectively. Besides, nano-scaled SLN-curcumin significantly inhibits the effect of cell-proliferation proteins including Mcl-1 and XIAP, and expression of anti-inflammatory cytokines such as TNF-α and IL-6 in the treatment of HL [73]. Guo and his research group reported that the synergistic effect of curcumin with doxorubicin showed remarkable results in the treatment of B cell lymphoma both *in vitro* and *in vivo* studies. They revealed that co-delivery of curcumin and doxorubicin (loading rate of curcumin and doxorubicin: 8.1 and 9.7 %) into xenografted mice reduced the invasive B cell lymphoma. They also stated that curcumin and doxorubicin combination *in vitro* significantly removed the invasive B cell lymphomas by regulating the apoptosis pathways [74]. Chen et al. [75] demonstrated that curcumin inhibited the invasion, mitigation, and cell proliferation activities and promoted the apoptosis in SU-DHL-8 cell line (diffuse large B cell lymphoma) by suppression and regulating the expressions of miR-21 and Von Hippel-Lindau (VHL) respectively. Similarly, *in vivo* study reported that curcumin suppressed the regulation of NF-κB signaling pathway and expression of pro-inflammatory cytokines in the treatment of Dalton's lymphoma cells by promoting the anti-oxidative defense system [76].

Aldehyde dehydrogenase (ALDH) is considered an imported enzyme in different types of cancer [31]. Li et al. [71] stated that 1 μM dose of curcumin effectively reduced the effect of Burkitt lymphoma cell lines as BL41−2 ($p < 0.0002$) and DG-75 ($p < 0.0377$) of about 50 % by inhibiting the proliferation, whereas by increasing the dose level up-to 15 μM, the 75 % reduction of THP-1 ($p < 0.0465$) was noted in ALDH-positive population. Another study revealed that curcumin effectively suppressed the expression of TNF-α mRNA in mantle cell lymphoma. It also observed that the inhibition of TNF-α cell leads to the inactivation of NF-kB and cell-proliferation factors which were then

neutralized by TNF-α antibody [77]. However, in the primary effusion lymphoma, curcumin significantly induced apoptosis and suppressed the activity of cell-proliferation by inhibition of the STAT-3 pathway [30].

5.2. Japanese apricot (Prunus mume)

Prunus mume (commonly known as Japanese apricot; *Rosaceae*) is considered as a good medicinal drug and food in Japan, Korea, and China. The recent evidence suggested that *Prunus mume* possesses several biological and pharmacological activities including inhibition of influenza A virus, anti-cancerous activities, suppression of pro-inflammatory factors, induction of apoptosis, and improvement of blood fluidity [78]. The accumulated data suggested that MK615 is an important and active ingredient/extract isolated from *Prunus mume* which holds multiple cyclic triterpenes including ursolic acid, betulinic acid, oleanolic acid are known for their anti-cancerous and anti-inflammatory activities, the structures are represented in Table 2 [79]. These triterpenes are active inhibitors that released pro-inflammatory cytokines (TNF-α, IL-6, and IL-8). Cytokines inhibition is based on MK615-induced inhibition by NF-κB pathway activation [80]. Inoue et al. [79] reported that MK615 exhibit significant anti-cancerous activity in a concentration-dependent manner against BALM-3 lymphocytic cell lines in combination with bendamustine. They also stated that combined administration of 25 μg/mL of bendamustine with 7.5 μg/mL of MK615 for 48 h treatment significantly showed the cytoplasmic blebbing, chromatin condensation, nuclear fragmentation, expression of Annexin-V and reduction of caspase-3 in BALM3 cells, which results in a noteworthy reduction of BALM3 cells of about 34.15 % as compared to alone MK615 treatment (1.11 %). Tsuji et al. [81] also found that *P. mume* ethanolic extract stimulates innate immunity which helps in the enhancement of immune function. Yanaki et al. [82] stated that MK615 significantly downregulated the expression of PD-L1 on tumor cells and showed a prolonged survival activity in a BL6/B16 mouse that disclosed the T cell-mediated anti-cancerous immunity. Similarly, Al-Jahdari and co-workers observed that the combination of MK615 with X-ray radiations protected CD4/CD8 T-cells and displayed the remarkable antitumor ability [83].

5.3. Resveratrol

Resveratrol (3,540-trihydroxystilbebe) is belonging to non-flavonoid polyphenol class called stilbenes. It is derived from several plant and beverage sources including grapes, berries, plums, peanut, and red wines (see Table 2) [84]. According to emerging data, resveratrol possesses several properties including anticancer, anti-inflammatory, anti-oxidant, and antiaging activities [85]. Meng et al. [86] reported that considerable administration of resveratrol (20 μM) effectively reduced cell-proliferation activity in HL-60 and NB-4 cells by enhancing the expression of a caspase-3 pathway. They also revealed that during the treatment of HL-60 cells, resveratrol increased the expression of PTEN mRNA and decreased the activity of p-AKT pathway. Kong et al. [87] demonstrated that the analog of resveratrol (pterostilbene) significantly induced apoptosis in the treatment of diffuse large B-cell lymphoma cell lines (DLBCL). They also reported that pterostilbene arrest the cell cycle at G1 phase in the reduction of DLBCL cell lines by inhibiting the cyclin-dependent kinase-2 (Cdk-2) and increasing the effect of check-point dependent kinase-2 (Chk-2). Zunino and his research group revealed the effect of resveratrol against human B lymphocytes (BL), they stated that during the treatment of B lymphocytes cell resveratrol showed dual behaviors at different concentrations. At 5 μM, resveratrol increased the cell-proliferation of $CD19^{+}$ BL, whereas resveratrol administration of 10 μM significantly suppressed the cell proliferation of $CD19^{+}$ BL and resultingly enhanced the expression of caspase-3 activation [88]. Radwan and co-workers revealed that resveratrol effectively promoted the activity of human leukocyte antigen (HLA) class II proteins family (DM and DR) during the treatment of B cell lymphoma (BCL). They also observed that resveratrol enhanced the processing of HLA class II-mediation by altering the response of thiol reductase and endo-lysosomal cathepsins including B, D, and S during the treatment of BCL [89]. Another study conducted by Ko et al. [90] reported that resveratrol reduced the mass of anaplastic large cell lymphoma (ALCL) by regulating the expression of markers including CD8, CD3, and CD2, present on the surface of ALCL. They also observed that resveratrol significantly up-regulated the expression of death receptors like Fas during the treatment of SR-786 cell line of ALCL.

Faber and Chiles, [91] demonstrated that 25 μM concentration of resveratrol in lymphocyte cell lines including OCI-Ly-1 and OCI-Ly-18 significantly induced the cell cycle arrest in S-phase. Another study reported that 24–32 μM consumption of resveratrol induces apoptosis in SUDHL-4 and NU-DUL-1 cell lines by the activation of Bax/Bcl2 pathway [87]. Jara and co-workers determined the anti-proliferated effect of resveratrol on Ramos cell line of Burkitt lymphomas by estimating its cell viability through MTT and Trypon Blue exclusion assay at different concentrations after 24 and 48 h treatment respectively. Both MTT and Trypon Blue exclusion assays revealed that maximum anti-proliferative activity of resveratrol against Ramos cell line was found after 48 h treatment with 150 μM concentration [92].

5.4. Pineapple (Ananas comosus)

Pineapple (*Ananas comosus*) is one of the most popular tropical fruit in the world. Pineapple is a member of the *Bromeliaceae* family [93]. Bromelain is an active protease and isolated from stem and fruit of pineapple as presented in Table 2 [94]. Bromelain exhibits several biological properties including anti-inflammatory, antibiotic, anti-cancer, anticoagulative, anti-thrombotic, and anti-edematous activities [95]. *In vitro* experiment showed that bromelain treatment to T cell eliminated the leu8/LAM1, CD8, CD44, CD6, and MIC2 molecules and promoted the expression of CD2 to activate T cell [96]. Another study demonstrated that bromelain effectively inhibited the regulation of CD25 surface molecules and blocked the expression of $CD4^{+}$ T cells. Furthermore, bromelain inhibited the expression of ERK_2 during the activation of T-cells [97].

Debnath and co-workers studied (*in-vitro)* the effect of bromelain in combination with peroxidase (BM-PR) against Dalton's lymphoma (DLA) cells and reported that BM-PR significantly suppressed the cell-proliferation at a dose of 500 μg/mL after 72 h treatment. They also suggested that BM-PR combination effectively inhibited the expression of an anti-apoptotic protein (Bcl-2), and enhanced the activity of apoptotic proteins including p-53, cytochrome-c, and Bax during the treatment of DLA [25]. Another study also founded that p53 expression in DLA cells was very low. But after treatment with bromelain plus peroxidase, the expression of p53 was significantly increased [26]. A similar study reported that bromelain and N-acetylcysteine proved as an important constituent in the treatment of human lymphoma cells by suppressing the expression of p-38 protein and activating the abnormal cell cycle progression [28,98]. Debnath et al. [25] reported that the administration of bromelain with peroxide (50 mg/kg; body weight) significantly reduced the activity of anti-apoptotic proteins including NF-kB and Bcl-2, and increased the expression of pro-apoptotic proteins like p-53, Bad, and Bax against non-Hodgkin lymphoma. Debnath et al. [99] showed that bromelain (*in vivo*) treatment in combination with peroxidase significantly promoted the expression of Bax, Bad, and cytochrome c and down-regulated the expression of NF-κB and Bcl-2 protein family during the treatment of Dalton's lymphoma cells (DLA) in mice and suggested as good therapeutic agent.

5.5. Annona fruits

Annona fruits belong to *Annonaceae* family that enriched with phenolic compounds such as phenolic acids, flavonoids, stilbenes,

Table 3
The *in vivo* and *in vitro* studies of active compounds with a mechanism of action in the treatment of lymphomas.

Plant	Active compound	Study type	Lymphoma/cell lines	Dose	Mechanism	Reference
Curcuma longa	Nano-scaled TPGS-curcumin and SLN-curcumin	*In vivo*	Hodgkin's lymphoma/ L-540	10−40 μM	Inhibit cell-proliferation and enhance the expression of anti-inflammatory cytokines (TNF-α and IL-6)	[73]
Curcuma longa herb root	Curcumin	*In vitro*	Cultured glioblastoma cells/ U-87MG and U-251MG	20 μM	Inhibit PI3K/Akt/mTOR pathway	[70]
Curcuma longa	Curcumin	*In vitro*	Hodgkin's lymphoma cells/ KM-H2, L-428, and L-1236	25 μM	Inhibit NF-κB and STAT3 activation. Suppress cell proliferation and induce apoptosis	[72]
Prunus mume (Japanese apricot)	MK615	*In vitro*	B-lymphoma/BALM-3	7.5 μg/mL	Synergize with bendamustine to induce apoptosis and suppress cell-proliferation	[79]
Prunus mume	MK615	*In vitro*	T-cell leukemia/ Su9T01and S1T cells	45.9 μg/mL	Inhibit cell-proliferation	[127]
Vitis vinifera, *Vaccinium macrocarpon*	Resveratrol	*In vitro*	Human leukemia (HL)/ HL-60	20 μM	Inhibit cell-proliferation, increase expression of caspase-3 pathway	[86]
Vaccinium macrocarpon	Resveratrol (pterostilbene)	*In vitro*	B-cell lymphoma cell lines (BCL)/ SUDHL-4, NU-DUL-1, OCI-LY8, and TMD8	12.5–100 μM	Induce apoptosis, and arrest the cell cycle at G1/ S phase	[87]
Vaccinium macrocarpon	Resveratrol (pterostilbene)	*In vivo*	B-cell lymphoma cell lines (BCL)/OCI-LY8	30 mg/kg/20 days	Inhibits the growth of implanted OCI-LY8 cells in a xenograft mouse model	[87]
Vitis vinifera	Resveratrol	*In vitro*	B lymphocytes (BL)/CD19 + BL	10 μM	Suppress the cell proliferation, and increase expression of caspase-3 pathway	[88]
Annona reticulata	HEEAM	*In vivo*	Dalton's lymphoma ascites (DLA)/Swiss albino mice	400 mg/kg/ body weight	Decrease the PCV and arrested the tumor growth	[103]
Annona muricata	Phenolics, flavonoids, and tannins	*In vitro*	Lymphoma/ Ramos-1	200 μg/mL	Suppress the cell-proliferation	[14]
Annona macroprophyllata	Polyphenols	*In vivo*	Human leukemic monocyte lymphoma cells/ U-937	4.38 mg/kg/ body weight	Synergize with geranylgeraniol to inhibit the mitochondrial complex I, and anti-proliferation	[104]
Pineapple (*Ananas comosus*)	Bromelain	*In vivo*	Leukemia/P-388	12.5 mg/kg/ body weight	Trigger the action of T cytotoxic cells, and angiogenesis	[128]
Pineapple (*Ananas comosus*)	Bromelain	*In vivo*	Non-Hodgkin lymphoma (NHL)/ DLA	50 mg/kg/ body weight	Synergize with peroxide to modulate the activity of apoptotic proteins, and up-regulate the antioxidant enzyme	[25]
Pineapple (*Ananas Comosus*)	Bromelain	*In vitro*	Dalton's lymphoma (DLA)	500 μg/mL/ 72 h	Synergize with peroxidase to inhibit proliferative activity, induce apoptosis	[25,26]
Camellia sinensis	Green tea (epigallocatechin-3-gallate)	*In vivo*	Human leukemia (HL)/HL-60 (human xenografted SCID mice)	100 mg/kg/ body weight	Synergize with quercetin to inhibit the activity of anti-apoptotic proteins (Bcl-2 and Mcl-1) and increase the expression of pro-apoptotic proteins (Bax)	[29]
Camellia sinensis	Epigallocatechin-3-gallate	Clinical trial	Non-Hodgkin lymphoma (NHL)	3.5 cups/day	Induce apoptosis	[111]

coumarins, tannins, and lignins. Annona fruits have strong antioxidant and anticancer activities because of their polyphenolic content (flavonoids, stilbenes, and coumarins) (see Table 2) [100]. The presence of phenolic compounds protect against the development of NHL because lower intakes of antioxidants linked to a compromised immune system [14]. According to the emerging evidence, *Annonaceous acetogenins* is an important active compound derived from the seeds of Annona, considered as a good potent therapeutic agent against several cancer cell lines [101]. A study conducted on *A. reticulata* and *A. squamosa* (species of Annona fruit) revealed that consumption of fruit helps in the treatment of adult T-cell leukemia/lymphoma (ATL) malignancy caused by human-cell lymphotropic virus type I (HTLV-I) [102]. Al-Shaya et al. [14] demonstrated that the chloroform extract of *Annona muricata* significantly suppressed the cell-proliferation of about 95 % in a dose-dependent manner (200 μg/mL; $p < 0.05$) against lymphoma cell line of Ramos-1. Similarly, Nalini and Durairaj, [103] revealed that hydroethanolic extract of *Annona muricate* showed high anti-lymphoma activity at 400 mg/kg (body weight) in Dalton's lymphoma ascites (DLA)-induced tumor models in a dose-dependent manner ($p < 0.05$). Recently, a study conducted by Calzada and co-workers revealed that *Annona macroprophyllata* and geranylgeraniol showed the maximum anti-lymphoma (human leukemic monocyte lymphoma cells) inhibitory concentration (EC_{50}) value of 1.07 and 4.38 mg/kg for Balb/c male mice, and 1.33 and 3.66 mg/kg for female mice respectively [104]. Similarly, Vikas et al. [105] extracted *Annona squamosa* by four different solvents (ethyl acetate, chloroform, methanol, and petroleum ether) and revealed that petroleum ether extract showed better cytotoxicity in leukemic K-562 cells and significantly reduced the mass of Dalton's lymphoma ascites (DLA) along with breast, lung, and nasopharyngeal cancer.

5.6. Green tea (*Camellia sinensis*)

Green tea is one of the important drinks taken by Chinese and Japanese over the thousands of years and derived from the leaves of *Camellia sinensis*. Polyphenols including flavonoids are the strongest antioxidant, anti-cancer, and anti-inflammatory agents in green tea. Epicatechin gallate, epigallocatechin-3-gallate (EGCG), epigallocatechin, and catechin, are the important active compounds in *C. sinensis* (see Table 2) [106]. A study showed that green tea (catechins) effectively robust the immune response against cancer by promoting the expression of natural killer and $CD4^+$ T cells. Furthermore, 4′-hydroxyl consider as a critical factor not only for promoting the activity of natural killer cells but also enhancing the expression of $CD4^+$ T cells *in vivo* [107]. Another study revealed that EGCG significantly boosts the immune response against tumor cells by enhancing the quantity of $CD8^+$ and $CD4^+$ T cells and reducing the accommodation of myeloid-derived suppression cells (MDSC) [108].

Long-term consumption of green tea increased the activity of xenobiotic-metabolizing enzyme glutathione S-transferase (GST), which helped in the inhibition of NF-κB transcription factors, and provide protection against B- cell lymphomas [109]. Calgarotto and his research group revealed that a combination of polyphenols including green tea and quercetin reduced the tumor growth (HL-60) in human xenografted

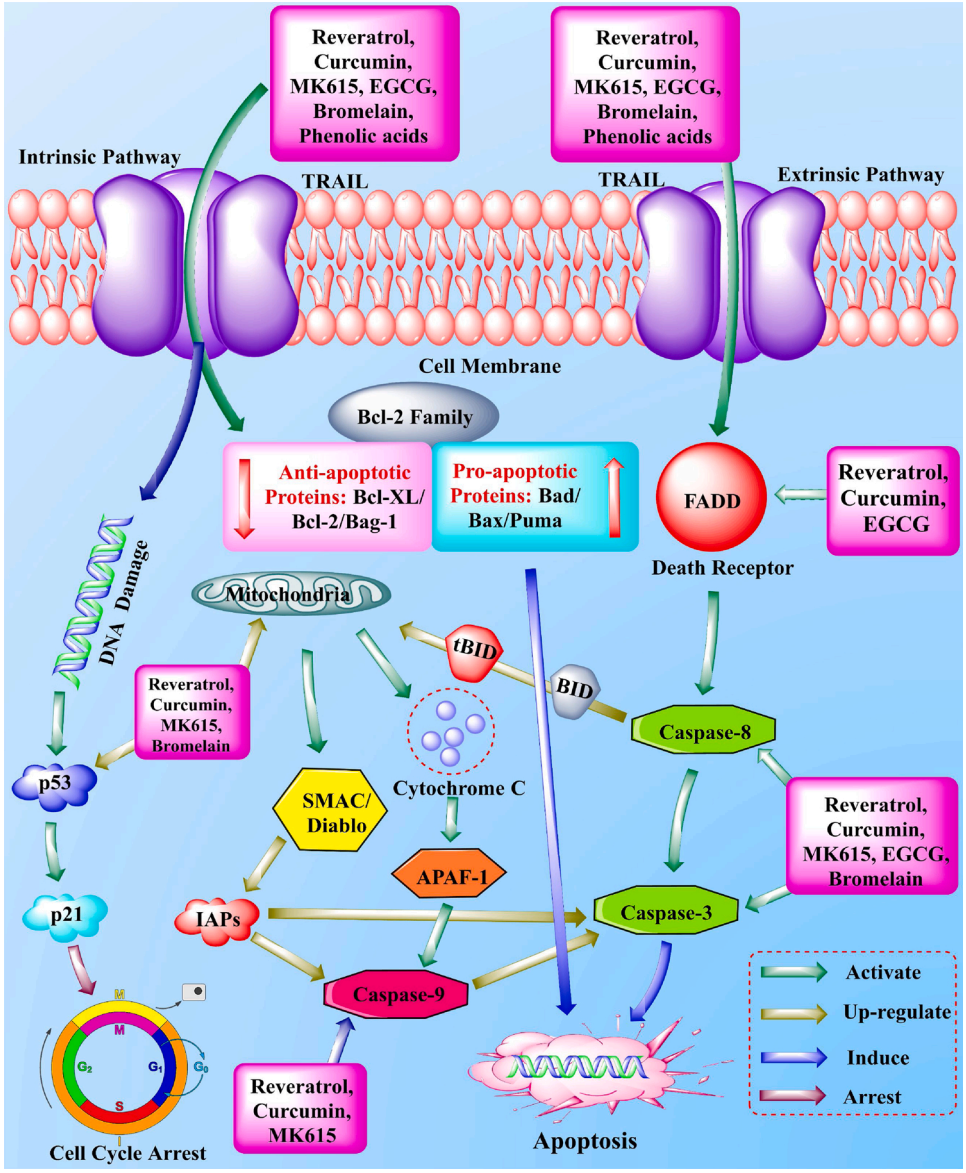


Fig. 2. The schematic diagram of apoptosis and cell cycle arrest by biomolecules in the treatment of lymphoma. TRAIL (Tumor-necrosis-factor Related Apoptosis-Inducing Ligand; purple); Bax (Bcl-2-associated X protein; sky box); Bcl-2 (B-cell lymphoma 2; pink box); Bak (Bcl-2 homologous antagonist killer; sky box); FADD (Fas-Associated protein with Death Domains; red circle); SMAC (Second Mitochondrial Activator of Caspase; yellow); BID [BH3 (Bcl-2 Homology-3)- Interacting Domain death agonist; light blue]; and APAF-1 (Apoptosis Activator Factor-1; orange); and IAPs (Inhibitor of Apoptosis proteins; red box).

SCID mice *via* inhibiting the activities of anti-apoptotic proteins (Bcl-2 and Mcl-1) and increase the expression of pro-apoptotic proteins including Bax. They also reported that consumption of green tea and quercetin activates the caspase-3 pathway to a greater extent and arrests the cell cycle (G1 phase) in HL-60 xenografted cells [29]. In another study, it has been proven that consumption of epigallocatechin-3-gallate (EGCG) showed significant effects against aggressive B-cell lymphoma by inhibiting the cell-proliferation and inducing apoptosis [110]. Similarly, Mirtavoos-Mahyari et al. [111] found that higher consumption of green tea (nonfermented) was associated with a 39 % reduced risk of NHL.

The summary of different plants with their active compounds against different lymphomas are presented in Table 3, and the schematic representation of apoptosis and cell cycle arrest in lymphomas are depicted in Fig. 2.

6. Conclusion

Lymphoma is considered a heterogeneous group of malignancies. Several conditions are exhibited by patients suffering from lymphoma, starting from mild fever to severe condition. However, timely diagnosis is required to subclassify and proper treatment plans against lymphoma. Biochemical parameters (serum LDH and cytokine estimation) and biopsy techniques are used for diagnostic purposes. Genetic disordered, bacterial, and viral infections and environmental factors are associated with the rising incidences of lymphoma. According to the data of present review, it is revealed that natural products (Curcuma longa, *Prunus mume*, *Vitis vinifera*, *Annona reticulata*, *Ananas comosus*, and *Camellia sinensis*) proved as a valuable therapeutic option against different types of lymphomas including NHL, HL, B-cell lymphoma, Dalton's lymphoma, and Burkitt lymphoma by inhibiting cell-proliferation, metastasis, inducing apoptosis, angiogenesis, suppressing PI3K/Akt/mTOR pathway, and activation of NF-κB and STAT3 pathways. The *in-vitro* study of Annona fruit (*Annona muricata*) showed the highest results of about 95 % in the reduction of lymphoma cell line Romas-1 in a dose-dependent manner. Similarly, *in vivo* study of curcumin reported a 50.5 % of reduction of Hodgkin lymphoma by inhibiting cell-proliferation proteins (Mcl-1 and XIAP). The present review findings proved natural products as a promising option to treat lymphoma and lead to the development of other natural active drugs. However, further examination is required to conduct the clinical trials to understand the exact mechanism of action of natural drugs on human body and to

isolate the more active constituents from other medicinal plants. It is also recommended to conduct further study on other species of plants in the near future to find optional human benefits concerning lymphomas.

Consent for publication

For this type of study informed consent is not required.

Funding

None.

CRediT authorship contribution statement

A. Hazafa, Hafiz M.N. Iqbal and S. Ahmad: Conceived the presented data, Writing - original draft, Software, Supervision. **A. Batool, M. Imran and H.A. Khan:** Developed the theory, Formal analysis, & Investigation. **Hafiz M.Z. Abideen and A. Zafar:** Revision and Editing.

Declaration of Competing Interest

All authors declared no conflict of interest.

Acknowledgements

Hereby, we extend our gratitude to A.Q Research Group, Pakistan for reviewing the article and providing helpful comments.

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