





Review Article

Quercetin as a Novel Therapeutic Approach for Lymphoma

Saiedeh Razi Soofiyani,¹ Kamran Hosseini,^{2,3} Haleh Forouhandeh,⁴ Tohid Ghasemnejad,⁴ Vahideh Tarhriz ,⁴ Parina Asgharian ,^{5,6} Željko Reiner,⁷ Javad Sharifi-Rad ,⁸ and William C. Cho ⁹

¹Clinical Research Development Unit of Sina Educational, Research, and Treatment Center, Tabriz University of Medical Sciences, Tabriz, Iran

²Student Research Committee, Shiraz University of Medical Sciences, Shiraz, Iran

³Department of Molecular Medicine, Faculty of Advanced Medical Sciences and Technologies, Shiraz University of Medical Sciences, Shiraz, Iran

⁴Molecular Medicine Research Center, Biomedicine Institute, Tabriz University of Medical Sciences, Tabriz, Iran

⁵Department of Pharmacognosy, Faculty of Pharmacy, Tabriz University of Medical Sciences, Tabriz, Iran

⁶Drug Applied Research Center, Tabriz University of Medical Sciences, Tabriz, Iran

⁷Department of Internal Medicine, University Hospital Centre Zagreb, School of Medicine, University of Zagreb, Zagreb, Croatia

⁸Phytochemistry Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

⁹Department of Clinical Oncology, Queen Elizabeth Hospital, Kowloon, Hong Kong

Correspondence should be addressed to Vahideh Tarhriz; t.tarhriz@yahoo.com, Parina Asgharian; parina.asgharian@gmail.com, Javad Sharifi-Rad; javad.sharifirad@gmail.com, and William C. Cho; chocs@ha.org.hk

Received 23 May 2021; Revised 15 June 2021; Accepted 12 July 2021; Published 2 August 2021

Academic Editor: German Gil

Copyright © 2021 Saiedeh Razi Soofiyani et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Lymphoma is a name for malignant diseases of the lymphatic system including Hodgkin's lymphoma and non-Hodgkin's lymphoma. Although several approaches are used for the treatment of these diseases, some of them are not successful and have serious adverse effects. Therefore, other effective treatment methods might be interesting. Studies have indicated that plant ingredients play a key role in treating several diseases. Some plants have already shown a potential therapeutic effect on many malignant diseases. Quercetin is a flavonoid found in different plants and could be useful in the treatment of different malignant diseases. Quercetin has its antimalignant effects through targeting main survival pathways activated in tumor cells. *In vitro/in vivo* experimental studies have demonstrated that quercetin possesses a cytotoxic effect on lymphoid cancer cells. Regardless of the optimum results that have been obtained from both *in vitro/in vivo* studies, few clinical studies have analyzed the antitumor effects of quercetin in lymphoid cancers. Thus, it seems that more clinical studies should introduce quercetin as a therapeutic, alone or in combination with other chemotherapy agents. Here, in this study, we reviewed the anticancer effects of quercetin and highlighted the potential therapeutic effects of quercetin in various types of lymphoma.

1. Introduction

The lymphatic system has important functions such as maintaining tissue fluid homeostasis, initiating humoral and cellular immune responses, and transporting intestinal lipids to the blood [1]. According to the classical theory of metastasis, malignant cells that reach the sentinel lymph nodes may

spread further into the distal lymph nodes, and subsequently form organ metastases [2]. Traditionally, four treatment methods including surgery, radiotherapy, chemotherapy, and immunotherapy are used alone or in combination to treat patients' malignant diseases [3, 4]. Chemotherapy is used as a common approach for the treatment of these patients; however, drug resistance is the key reason for

decreased effectiveness of chemotherapy and occurs due to adaptation of cancer cells to chemotherapy agents [5]. The development of analytical tools, genome extraction, engineering strategies, and microbial science have opened a new window on the sciences of pharmacotherapy and cancer therapy. Given this development, in relation to cancer and some infectious diseases, their natural products and structural analogues are of great help to researchers in the field of pharmacology [6]. Producing substances which are capable of killing malignant cells without being toxic is important and has attracted increasing interest. In recent years, it has been shown that some substances derived from plants can have beneficial effects on malignant cells [7–10]. Flavonoids have been the most studied. They interact in specific stages of the carcinogenesis process to prevent cell proliferation and consequently cause apoptosis [11–15]. Quercetin (3,3', 4', 5,7'' penta-hydroxyl flavones) is a polyphenolic flavonoid found in apples, red grapes, onions, raspberries, honey, cherries, citrus fruits, and green leafy vegetables [16].

In recent years, several studies have demonstrated that quercetin has different biological effects [17], including antiviral, cell-cycle modulation, inhibitory effects on antioxidant angiogenesis, anticancer, apoptosis-inducing induction, and C-blocking protein kinase [18–20]. It was suggested that chronic daily intake of quercetin might prevent some types of malignant diseases as well as lymphoid cancers. Several pathways have been identified that are affected by quercetin in various malignancies [21, 22]. Here, for the first time, we reviewed the anticancer and therapeutic effects of quercetin in different types of lymphoid cancers.

2. Lymphomas and Possible Causes of Increased Lymphoma

The lymphatic system is essential for immune response, maintaining tissue fluid balance, transporting antigen and antigen-presenting cells (APCs) to the lymph nodes, and transporting lipids absorbed from the intestine into the blood. Therefore, disorders of the lymphatic system can cause lymphedema, compromise local immune response, and cause intestinal malabsorption [23]. The lymphatic system includes the lymph nodes, spleen, thymus, and bone marrow. Lymphomas can affect all of them as well as other organs. Lymphoma is a malignant disease of the lymphatic system. There are several types of lymphoma: Hodgkin's lymphoma (formerly called Hodgkin's disease) and non-Hodgkin's lymphoma [24]. Causes and risk factors that increase the susceptibility to lymphoma include age (people over 60), gender (more prevalent in women than men), obesity, ethnicity (e.g., high percentage within white Americans), exposure to chemicals or radiation (such as pesticides and nuclear radiation), infections (such as HTLV-1 virus, *H. pylori*, hepatitis C, and EBV), autoimmune diseases (such as RA and celiac disease), immune deficiencies (such as AIDS), or receiving immunosuppressive drugs [25–27]. The role of the lymphatic system in the progression of metastasis of malignancies has attracted an increased interest in the last 15 years [28]. The lymphatic system also plays a critical role

in cancer progression, because the metastatic cancer cells can spread through the lymph vessels to the lymph nodes [23]. The most common sites of solid tumor metastases are lymph nodes. Their presence indicates a poor prognosis and usually suggests the need for systemic treatment in patients with malignant disease. On the other hand, the presence of cancer cells in the lymph nodes may reflect the ability of the primary tumor to metastasize; however, their actual presence in the lymph nodes may be inconclusive [29, 30]. This reasoning indicates that lymph node metastases need to be treated for prevention of distant metastasis and ultimately eradication of the disease [31–33]. The metastases in lymph nodes might indicate whether there is a possibility of further expansion of the malignancy in lymph nodes or whether distal metastases have already occurred [34]. Lymph node metastasis is thought to be regulated in two stages; the first one being the uptake of malignant cells into the lymph vessels and the second one a successful penetration of these cells into lymph nodes [35]. Because of the lack of functional lymph vessels in tumor cells, interstitial fluid pressure increases and the lymph flow to the lymph nodes changes, which causes the tumors to drain [36]. Tumor-induced VEGF-C and VEGF-D increase the proximal contraction of lymphatic vessels [37]. The expansion of malignant cells to the lymph nodes is decreased when tumor-induced lymph vessel regeneration is prevented [36, 38–40].

3. Quercetin and Its Antitumor Effects

Despite great advances in the treatment of malignant diseases, they are still recognized as life-threatening diseases. However, the effects of chemotherapy which is used as a common treatment for many malignant diseases are limited because of resistance to this type of therapy and serious adverse effects. Today, natural compounds such as quercetin are recognized as an important factor in malignant disease prevention and treatment because of their effects, high therapeutic potential, and low toxicity [41]. Quercetin, as a lipophilic compound, can cross cell membranes and initiate several intracellular signaling pathways. Quercetin's unique characteristic includes its dual function as a peroxidant or antioxidant [42]. It seems that quercetin can act as a potential antiproliferation and antimalignant as well as apoptosis inducer (Figure 1) [41, 43]. The mitochondrial-mediated pathway has been suggested as the main mechanism by quercetin to induce apoptosis [44–46]. It also induces apoptosis by increasing proapoptotic molecules such as Bax, caspase-3, caspase-9, p53, or decreasing of antiapoptotic substances [47]. Quercetin prevents the cell cycle by reducing D1/Cdk4 and E/Cdk2 and regulating p21, which ultimately stops the G1 cell cycle [48]. Quercetin binds directly to tubulin and eliminate the polymerization of cell microtubules, which causes stopping of the cell cycle [49]. It seems that quercetin interferes with a large variety of molecules involved in the cell cycle. The complex of PI3K/AKT/PKB is a pathway involved in different processes such as regulation of cell survival, cell cycle, growth progression, and carcinogenesis [50]. This pathway can be targeted with quercetin in different types of malignancies and cause induction of apoptosis, inhibition

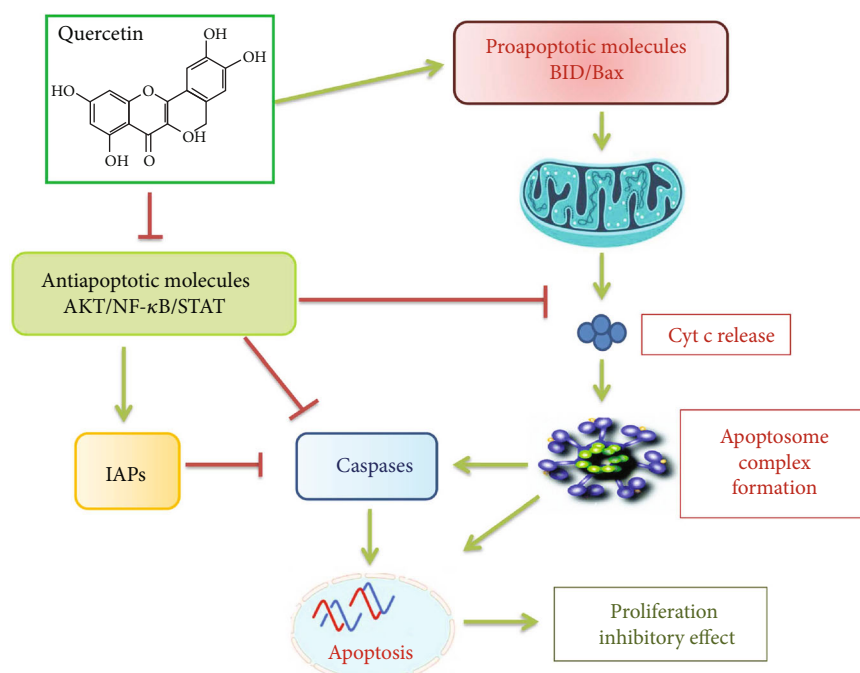


FIGURE 1: Suggested model for quercetin effects on lymphoma cells. Quercetin inhibits cell growth by apoptosis induction via inhibitory effects on antiapoptotic signaling molecules and proapoptotic protein induction which cause activation of mitochondrial-mediated caspase activation and apoptosis [43, 51, 59, 60].

of cancerogenesis, and development of malignancy [51]. Numerous studies have reported that quercetin causes phosphorylation and stabilization of p53 levels. p53 is considered to be a key molecule in the proapoptotic and antimalignant effects of quercetin [52]. p53 has an antioxidant effect through regulating several genes, including aldehyde dehydrogenase ALDH4A1, Mn-SOD2, microsomal GSH homologous transferase PIG12, Gpx1, and catalase [53–55]. A decrease in p53 sensitizes cells to H_2O_2 damage, which causes decreased viability and increased apoptosis and DNA oxidation. The function of P53 in malignant cells is significantly blocked by poor regulation of its genes [56]. Increased ROS as oxidative stress causes DNA damage and mutations. Quercetin can reduce ROS by electron donation that leads to reduce ROS-mediated DNA damage [57, 58]. According to the results of related studies, it could be concluded that quercetin has an important role to treat and control malignancies. Regulation of cell-cycle-related proteins, antioxidant effects, induction of apoptosis, and induction of cell-cycle arrest are some of the mechanisms by which quercetin has its effects in the treatment and inhibition of malignancies.

4. Molecular Targets of Quercetin in Malignant Cells

Malignant diseases have an abnormal activation of various survival signaling pathways, e.g., a different antiapoptotic protein expression [61]. Aberrant activation of signaling pathways such as serine-threonine kinase, activator protein 1 (AP-1), AKT kinase/protein kinase B (AKT/PKB), nuclear factor kappa B (NF-κB), mitogen-activated protein kinase

(MAPK), androgen receptor, Raf/Ras pathways, and estrogen receptors are the key mechanisms that can cause tumorigenesis [62, 63].

Tyrosine kinases like Jak and Src kinases are activated in malignant cells [64]. These signaling transductions are essential for normal cell proliferation and physiological function. In malignant cells, deregulated expression of these pathways results in abnormal cell growth and apoptosis resistance. Several studies have been conducted to explore the strategies of targeting the overactivated molecules involved in survival pathways to induce apoptosis in malignant cells [16]. It has been shown that quercetin inhibits cell growth by cell-cycle arrest and induces apoptosis in different malignant cells by targeting different molecular pathways such as activation of NF-κB and signal transducers/activators of transcription STAT3 (Figure 2) [65–68]. It can also downregulate the expression NF-κB, Bcl-2, cyclooxygenase 2 (COX-2), matrix metalloproteinase 9 (MMP-9), tumor necrosis factor (TNF), cyclin D1, and adhesion molecules [69–73]. NF-κB is one of the important transcription factors identified in the nucleus of B lymphocytes and plays a critical role in regulating the function of the human immune system. This transcription factor controls the expression of many genes and has been linked to inflammatory, neurological, and cancer diseases [74]. Numerous studies have shown that NF-κB activation is associated with some lymph node diseases, including large cell lymphoma, Burkitt's lymphoma, diffuse large B-cell lymphoma, fibrosarcoma, Hodgkin's lymphoma, mammary carcinoma, and mantle cell lymphoma melanoma [75].

Several research indicated that the chemopreventive/chemotherapeutic effects of quercetin are based on its

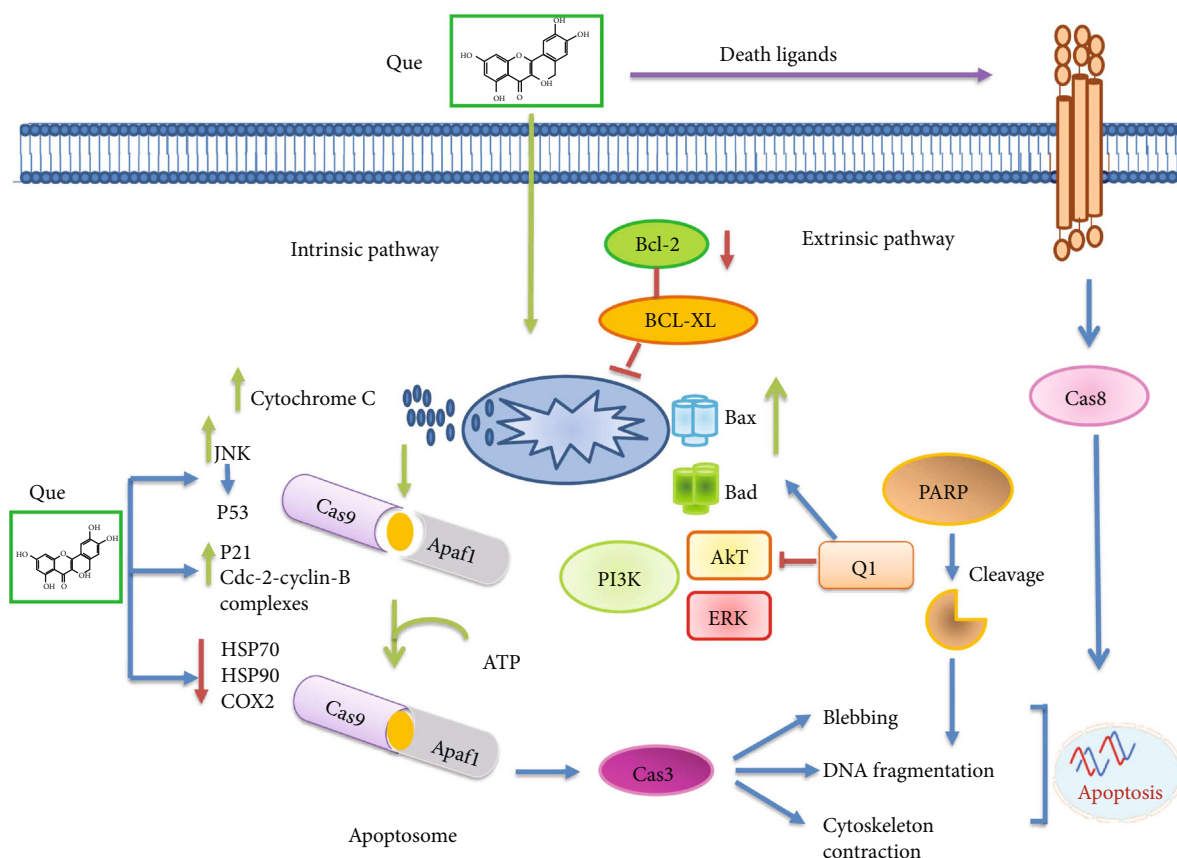


FIGURE 2: A view of the effect of quercetin on the expression level of genes involved in apoptosis pathway [65–68].

concentration. At low doses, quercetin acts as an antioxidant. However, at high doses, quercetin has effects of a prooxidant and prompts chemotherapeutic effects. The antitumor effects of quercetin are related to its potential in reducing tumor growth, inducing apoptosis, promoting cell-cycle arrest, and suppressing mitotic processes, which are performed by modulating cyclin, proapoptotic, PI3K/AKT, and mitogen-activated protein kinase (MAPK) molecular pathways (Table 1) [76]. Quercetin also downregulates p-ERK1/p-ERK2 in the multiple myeloma (MM) cell lines which results in inhibition of MAPK pathway activation and suppression MM cell proliferation.

5. Quercetin and Lymphomas

5.1. Multiple Myeloma and Quercetin. Multiple myeloma is characterized by accumulation of plasma cells in the bone marrow and an increased monoclonal protein concentration in blood and/or urine [89]. The effects of quercetin on multiple myeloma cells have been reported in several studies [85, 86, 90]. The deregulation of apoptosis in plasma cells plays a key role in the pathogenesis and chemoresistance of multiple myeloma. Quercetin inhibits IQ motif-containing GTPase activating protein 1 (IQGAP1) expression in multiple myeloma cells. IQGAP1 activates growth factor-mediated activation of extracellular signal-regulated kinase (ERK) and mitogen-activated protein kinase (MAPK)/ERK kinase (MEK). The RAS/MEK/ERK signaling pathway plays

a key role in MM pathogenesis [86]. Xu et al. demonstrated that quercetin activates the apoptosis-related proteins and induces cell-cycle arrest in MM cell lines. It also upregulates the apoptosis-related proteins including caspase-3, 8, and 9; upregulates PARP; and inhibits Bcl-2 expression. Quercetin induces the expression of P53, P21, and P27 and reduces the phosphorylation levels of p-ERK and p-AKT in MM cell lines [85].

5.2. Quercetin and T-Cell Lymphoma. T-cell lymphomas are a group of diseases characterized by clonal expansion and dysfunction of T-cells. T-cell lymphomas have been classified into two groups: cutaneous TCL (CTCL) and peripheral TCL (PTCL) [91, 92]. The PI3K/AKT pathway is the main target in antimalignant therapy and PI3K as a lipid kinase plays a key role in malignant cell transformation. PI3K is involved in regulating cell growth, survival, apoptosis, and angiogenesis. It also activates AKT which has a key function in both physiological and pathological signaling pathways. The anti-malignant effect of PI3K is based on inhibition in hematological malignancies via the blocking of survival signaling pathways within malignant and nonmalignant cells along with controlling cytokine secretion and activating the immune response. Maurya et al. indicated that in human leukemic cell lines, quercetin can inhibit upregulation of AKT1/2 and tensin homolog (PTEN) pathways by reducing PI3K/AKT activity and suppressing the proliferation in human leukemic cell lines. AKT induces cell survival by

TABLE 1: The effects of quercetin in treatment of lymphomas.

Dose	In vitro/ in vivo	Cell line	Effective molecular mechanism	Molecular targets of quercetin	Ref.
10 or 20 μ M	<i>In vitro</i>	U937	Arrests cell cycle in the G2/M phase, increases cyclin B protein levels, and decreases cyclin D and E and E2F1 and E2F2 levels	Cyclin B, cyclin D, and cyclin E	[77]
50 μ M	<i>In vitro</i>	Daudi and TMD-8	Decreases expression of Notch1 protein	Notch1 protein	[78]
—	<i>In vitro</i>	Namalawa	Arrest of cells in the G2/M phase	Caspase-3	[79]
20 μ M	<i>In vitro</i>	VAL, RL, and SUDHL-4 cell lines	Reduces expression of survivin and Mcl-1 and reduces restoration of the TRAIL pathway	TRAIL, Mcl-1	[80]
20 μ M	<i>In vitro</i>	DLBCL	Inhibits p-STAT3 and decreases expression of Mcl-1, survivin, and Bcl-x1 genes	STAT3 protein	[81]
50 μ M	<i>In vitro</i>	BC1, BC3, and BCBL1	Increases the number of G1 events; increases the inhibition of PI3K and mTOR kinase; reduces the Wnt activation pathway; decreases expression of c-FLIP, cyclin D1, c-Myc, and p65 NF- κ B; reduces the release of IL-6 and IL-10; increases expression of HLA II (HLA-DR); decreases expression of HLA I	c-FLIP, cyclin D1, c-Myc, IL-6, IL-10, KSHV proteins, HLA-DR, and calreticulin	[59]
50 mg 2.5, 10, and 25	<i>In vivo</i>	—	Increases and decreases expression of the <i>HIGD2A</i> gene	Higd2a protein	[82]
30 μ M	<i>In vivo</i>	—	Inhibits primary viral antigens	Ornithine decarboxylase (ODC)	[83]
50 and 100 μ M	<i>In vitro</i>	Raji cell	Inhibits PI3K δ ; decreases expression of cIAP-1, cIAP-2, and anti-/proapoptotic molecules; inhibits the mTOR pathway; increases expression of the γ H2A.X protein	PI3K and mTOR	[84]
100 and 200 μ M/L	<i>In vitro</i>	Raji, Akata, 2A8, Ramos, and BL-41	Inhibits c-Myc expression and the PI3K/AKT/mTOR pathway, reduces expression of HSP-70, and stimulates autophagy	c-Myc protein, PI3K, AKT, and mTOR	[60]
40, 80, 160, and 320 μ M/L	<i>In vitro</i>	NCL-H929	Inhibits CDK4 expression; downregulates p-ERK and p-AKT; activates apoptosis-related proteins caspase-3, caspase-8, caspase-9, and PARP	Caspase-3, caspase-8, caspase-9, PARP, Bcl-2, P53, P21, P27, CDK4, p-ERK, and p-AKT	[85]
—	<i>In vitro</i>	U266, KM3, RPMI8226, and MM	Downregulates IQGAP1 expression and p-ERK1/2 and inhibits the MAPK pathway in MM cells	IQGAP1 protein and ERK1/2	[86]
—	<i>In vivo</i>	—	Downregulates p-AKT, p-PDK1, p-BAD, p-GSK-3 β , p-mTOR, p-IkB α , VEGF-A COX-2, iNOS, and NO level. Upregulates p-PTEN	AKT, PDK1, BAD, GSK-3 β , mTOR, Ikb α , VEGF-A, COX-2, iNOS, and PTEN	[87]
300 μ M/L	<i>In vitro</i>	DLA	Downregulates p-AKT 1, p-PDK1, p-BAD, TNFR1, PKC α , and upregulates PTEN	AKT, PDK1, BAD, TNFR1, and PTEN	[88]

phosphorylating/inhibiting Bcl-2-associated agonist of cell death (BAD) which promotes cell death and apoptosis by its dephosphorylation. Therefore, BAD phosphorylation stimulates cell survival. Quercetin attenuates the PI3K/AKT pathway and prevents survival signals in lymphoma growth [88].

5.3. Quercetin and Large B Lymphomas (Hodgkin and Non-Hodgkin). Another type of lymphoma is the B-cell lymphoma, which is classified into Hodgkin's and non-Hodgkin's lymphomas. According to the World Health Organization (WHO), B-cell lymphomas are classified into five major categories: diffuse large B-cell lymphoma (DLBCL), follicular lymphoma, marginal zone B-cell lymphoma (MZL) or mucosa-associated lymphatic tissue lymphoma (MALT), small lymphocytic lymphoma (SLL), and mantle cell lymphoma (MCL) [93]. Aggressive lymphomas require serious treatment. On the other hand, this type of malignancy therapy depends on the type of lymphoma and the stage and grade of the disease. For example, slow-growing lymphomas can be treated with radiation therapy, but the aggressive type has to be treated with chemotherapy in addition to radiation therapy [94, 95]. Chemotherapy and radiation therapy have many adverse effects. Therefore, some researchers have tried to use therapies with fewer side effects, such as herbal compounds. One of these plant substances is quercetin, which is rich in polyphenols and flavonoids and has been shown to have anti-inflammatory, antimalignant, and antioxidant (free radical scavenger) effects [96–98]. Fil'chenkov et al. investigated the antiapoptotic effects of quercetin and resveratrol in vitro on B-cell lymphoma cell lines (Namalawa). Using flow cytometry and ¹H NMR spectroscopy, they found that these two substances activated caspase-3 apoptotic cycles and increased hypodiploid cells as well as the number of motile lipid domains. Thus, the combination with quercetin causes time-dependent arrest of cells in the G2/M phase [79]. Lee et al. studied the U937 lymphoma cell line and found that the main mechanism of inhibition of lymphoma cell growth is related to cell-cycle arrest in the G2/M phase and induction of the caspase-mediated apoptotic process. They found that quercetin stabilized U937 cells in the G2/M phase, which in turn increased cyclin B protein levels and decreased cyclin D, E, E2F1, and E2F2 levels, and vice versa. Quercetin stimulates cell death by modulating Bcl-2 and Bcl-xl without altering the expression of Bcl-2 and Bcl-xl proteins, and this action is mediated by caspase-3. Finally, quercetin makes time-dependent accumulation of U937 cells in the G2/M phase in which arrest occurs and increases the time-dependent cell population in the sub-G1 phase [77]. Frankenfeld et al. studied the association of dietary flavonoid intake with a reduced risk of developing non-Hodgkin's lymphoma (NHL). They found that consuming more flavonols such as quercetin, epicatechins, anthocyanidins, and proanthocyanidins reduces the risk by 47% in the highest quarter compared to the lowest (95% CI: 31%, 73%), and that the more flavonols were consumed, the lower was the risk of non-Hodgkin lymphoma [99]. Kawahara et al. studied lymphoma and leukemia cell lines, especially Daudi (Burkitt's lymphoma) and TMD-8 (diffuse large B-cell lymphoma), and found that cyclopamine and quercetin inhibited cell line

growth and stimulated apoptosis. Cyclopamine targets the Hh signaling protein called Gli1 and reduces its expression. Quercetin reduces the expression of Notch1 protein and its active component in the DND-41 lymphocytic T leukemia cell line. They concluded that these natural substances could be used as targeted treatment for chemotherapy-resistant lymphoma and leukemia [78].

Jacquemin et al. found that quercetin combined with TRAIL therapy could be beneficial for malignant diseases such as non-Hodgkin's lymphoma (NHL). They found that pretreatment of malignant cells with 20 μ M quercetin for 24 hours overcomes the resistance of lymphoma cell lines to tumor necrosis factor-related apoptosis-inducing ligand-(TRAIL-) stimulated cell death. This compound completely activates caspase-3, and then it activates caspase-8 and caspase-9. Using flow cytometric analysis, they have shown that quercetin pretreatment prevents the expression of TRAIL receptors in lymphoma cell lines such as RL and VAL. In these cells, quercetin increases the expression of caspase-10 following TRAIL stimulation, but it is not needed for the reversal of apoptosis. Quercetin sensitization is independent of caspase-10 and the regulation of TRAIL-RISC complex formation. Quercetin reactivates the caspase-independent mitochondrial pathway by reducing the expression of survivin and Mcl-1, except p53 [80]. Rituximab is a chimeric monoclonal antibody against the CD20 protein on the surface of B cells and causes cell death after binding of the ligand to the receptor. This drug is used in the treatment of non-Hodgkin's lymphoma (NHL), chronic myelocytic leukemia (CLL), autoimmune diseases such as rheumatoid arthritis (RA), and skin lesions caused by the EBV virus. Li et al. studied the effects of monoclonal antibody in combination with quercetin on DLBCL lymphoma cell lines (WUS-DLCL-2 and SUDHL-4). They found that by using the cell viability method, these cell lines are sensitive to 20 μ M quercetin; furthermore, by using flow cytometry, quercetin induces apoptosis in these cell lines. The amount of 20 μ M quercetin together with 5 μ g/ml of antibody increased the sensitivity of the cell lines to the rituximab antibody. They also found that antibody-induced apoptosis was amplified by quercetin on the cell lines, and the quercetin-antibody complex inhibited the p-STAT3 pathway (involved in the regulation of Mcl-1, survivin and Bcl-x1 genes) because the expression of these genes was significantly reduced [81].

In addition to the STAT3 signaling pathway, the PI3K/AKT/mTOR and Wnt/ β -catenin pathways can be inhibited by natural products such as quercetin. These pathways cause highly aggressive B-cell lymphomas, such as primary effusion lymphoma (PEL). The Granato research team found that quercetin induces the death of the BC1, BC3, and BCBL1 cell lines in a dose-dependent manner by increasing the number of G1 events and causing cell death by PARP cleavage. They also found that quercetin inhibited PI3K and mTOR kinase and reduced the Wnt activation pathway, which eventually caused cell death to occur by inhibiting PI3K/AKT/mTOR signaling. mTOR was less phosphorylated, and quercetin reduced AKT phosphorylation at the Ser473 position. Quercetin also decreased prosurvival molecules downstream of these pathways, such as c-FLIP,

cyclin D1, and c-Myc, and it reduced nuclear localization of p65 NF- κ B. They showed that protein phosphatase inhibitors neutralized dephosphorylation of tyrosine STAT3 by quercetin in the BC3 cell line, and since it has two-way communication between these pathways, it seems that quercetin reduces the release of the IL-6 and IL-10 cytokines. According to them, quercetin regulates the autophagy process by inhibiting the mTOR pathway and the STAT3 pathway and reducing the expression of FADD-like IL-1 β -converting enzyme- (FLICE -) inhibitory protein (c-FLIP) and viral FLICE-Inhibitory Proteins (v-FLIPs) in the cell lines. In addition, the survival of BC3 and body-cavity-based lymphoma (BCBL1) cells is reduced by the quercetin-bortezomib complex and quercetin increases the activity of this proteasome inhibitor. Following the activation of T_H CD4⁺ cells, the expression of HLA II molecules (HLA-DR) in cells increases and the expression of HLA I decreases, and quercetin induces exposure to calreticulin on the surface of malignant cells [59].

Salazar et al. studied the *HIGD2A* gene (involved in cell survival under hypoxia) and its role in diffuse large B-cell lymphoma (DLBCL) by modulating the expression of this gene in mice. Using RT-qPCR analysis, they found that exposure to 50 mg/ml quercetin caused the expression of this gene in the bone marrow tissue (reduced hypoxia) of lymphoma mice. In addition, it increased in the liver and spleen tissue (increased hypoxia) due to the rapid proliferation of tissue, while in healthy mice, the expression of this gene in the bone marrow and spleen increased but it decreased in the liver. Finally, they found that *HIGD2A* gene expression increased in DLBCL cells and decreased in nodal marginal lymphoma (NMZL) [82].

5.4. Quercetin and Burkitt's Lymphoma. Another malignant disease of the lymphatic system is Burkitt's lymphoma. This type of malignancy is most often associated with B lymphocytes in the germinal regions [100]. Clinically, this malignancy is classified into three categories including the endemic or African variant in which the EBV virus infects children, the sporadic or non-African variant hosted by children, and the immune system defect-related variants that are often associated with HIV infection or in people who are immunocompromised [101–103]. These variants are often associated with mutations in c-Myc gene which is a regulator and protooncogene [104]. Risk factors for the disease include HIV/AIDS infection, posttransplantation immunosuppression, and malaria infection [105]. Treatment of this type of malignancy depends on the type of the disease. Nevertheless, the first line of treatment, depending on when the disease is diagnosed and whether the tumor is slow or fast growing, is the use of chemotherapy. Drugs which are used to treat Burkitt's lymphoma are cyclophosphamide, doxorubicin, methotrexate, rituximab, etc. In addition to chemotherapy, immunotherapy, bone marrow transplantation, stem cell transplantation, radiotherapy, etc., are also used for treatment [100]. Recently, herbal products with active ingredients have been used to treat this type of malignancy because they have less adverse effects. Based on their research on Raji cells (Burkitt's lymphoma cells), Okamoto et al. found that quercetin inhibited the stimulation of primary antigens (EA) by

the EBV virus which was induced by 12-O-tetradecanoyl phorbol-13-acetate (TPA). They also found that doses of 25, 10, and 2.5 μ g/ml of quercetin inhibited 82, 74, and 32% of primary viral antigens, respectively. Finally, they concluded that natural inhibitory substances such as quercetin may also be beneficial in increasing lymphoma inhibition by TPA [106].

Inadequate functioning of the PI3K pathway is involved in the growth and development of a variety of malignancies. As mentioned earlier, quercetin inhibits the PI3K pathway. Lim et al. studied a subset of a quercetin called fisetin. They found that because PI3K has several isoforms and is expressed in the Raji cell line (gamma and delta isoforms are expressed more on these cells than alpha and beta), tPI3K δ can be targeted by fisetin followed by induction of apoptosis. They also showed that fisetin reduced the expression of anti-/proapoptotic molecules. Therefore, using the immune-blotting technique, 30 μ M concentration of fisetin reduced cIAP-1 and cIAP-2 protein expression. It also inhibited the mTOR pathway by inhibiting phosphorylation of the mTOR pathway (S2448) and its downstream targets, p70S6K and 4E-BP1. Following this process, apoptosis increased in Raji cells. 30 μ M of fisetin also increased the expression of γ H2A.X protein (a marker of cell DNA damage), which in turn indicated the proapoptotic activity of this substance on Raji cells [84].

As mentioned earlier, one of the causes of Burkitt's lymphoma is overexpression of the c-Myc gene and its translocation. Granato et al. demonstrated that quercetin generally reduced and inhibited the c-Myc expression and the PI3K/AKT/mTOR pathway and induced cytotoxicity against Raji, Akata, 2A8, Ramos, and BL-41 as Burkitt's lymphoma cells. They found that quercetin reduced tumorigenesis in BL-41 cells because 50 and 100 μ M concentrations of this substance decreased c-Myc expression in BL-41, Raji, Akata, and Ramos cells. By phosphorylating 70S6K and 4E-BP1, the mTOR pathway was inhibited. The effect of quercetin-mediated toxicity on BL-41 and Ramos cells was greater than on Raji and Akata cells. Western blot analysis showed that quercetin was involved in PARP fragment cleavage in apoptotic cell death. The decreased expression of the c-Myc protooncogene and inhibition of the PI3K/AKT/mTOR pathway leads to BL-41 cell death. It seems that quercetin reduces the expression of heat shock protein (HSP-70) followed by a decreased expression of c-Myc protein in BL-41 cells. Quercetin also affects HSP-90 expression and decreases HSP-70 expression in Raji and Akata cell lines. Quercetin stimulates the autophagy process in BL-41 cells because the lipidation of cells (autophagy markers) treated with this substance is increased and the induction of the autophagy process helps to reduce c-Myc expression in some cell lines [60].

5.5. Antimalignant Effect of Quercetin (Molecular Mechanisms). Since it seems that quercetin has chemopreventive and chemotherapeutic effects in vivo and in vitro, it has been used as an antitumor drug. This natural product has antioxidant effects in small amounts and prooxidant effects in large amounts; therefore, it can be used as a chemotherapy drug by reducing malignant cell proliferation, apoptosis,

cell-cycle arrest, etc., through various molecular pathways that have become more and more interesting [107–109].

5.6. Role in Cell Proliferation. One of the main roles of quercetin is to inhibit the growth and proliferation of many types of malignant cells, including lymphoma, prostate, cervix, lung, breast, and colon. Quercetin can cause cell-cycle arrest in the G2/M phase or G1 phase, depending on the type of cancer cell [77, 110, 111]. Cyclins as well as kinase-dependent cyclins (cdks) play a major regulatory role in the cell cycle [112, 113]. The degree of cell inhibition depends on the concentration of quercetin and has often been studied in vitro [114]. Quercetin-mediated cell-cycle regulation can be interceded by p21, p27, p53, and Chk2 proteins. Regulation of reduced expression of Cdk1 and cyclin B1 as well as pRb phosphorylation can be shown on many types of malignant cell lines [115, 116]. As mentioned before, Granato et al. have investigated cell biology, growth, and proliferation of B lymphoma cells (including BC1, BC3, and BCBL1 cell lines) at different concentrations of quercetin [59].

5.7. Role in Oxidative Stress. Oxidative stress is caused by an imbalance between oxidants (such as ROS) and antioxidants (such as detoxification systems) [117]. Quercetin increases the activity of antioxidants by increasing the glutathione (GSH) level. GSH as a donor is involved in the conversion of H_2O_2 to H_2O by the enzyme superoxide dismutase (SOD). Quercetin stimulates GSH production [118]. The high activity of signaling pathways involved in cell survival, proliferation, and migration is directly related to oxidative stress. For example, ROS can activate the PI3K/AKT pathway, which in turn plays a crucial role in the growth and development of various malignancies [119]. According to Maurya et al., 300 μM of quercetin inhibited the increase of ROS production, which in turn phosphorylated the AKT, PDK1, and Bcl-2 promoters, followed by downregulation. In Dalton lymphoma ascite (DLA) cells treated with H_2O_2 , quercetin increased the level of PTEN protein [88].

5.8. Role in Autophagy. One of the natural cell mechanisms to remove unnecessary cell components is the process of autophagy, and due to this, the cell components are decomposed and recycled. This process helps to stimulate malignant growth by increasing the survival of malignant cells [120–122]. Several studies have shown that quercetin causes instability and does not induce autophagy in malignant cells. It also diminishes autophagy loss by reducing the stabilization of β -catenin and HIF-1 α and inhibiting the phosphorylation of AKT, mTOR, and ERK [76]. The STAT pathway (signal transducer and transcription activator) is associated with JAK family proteins and is also involved in mediating cellular responses to cytokines. In general, STAT3/5 is involved in the inflammatory and carcinogenic processes, and conversely STAT1 is involved in the inflammatory process [123]. Granato et al. found that quercetin induced autophagy in PEL cells by inhibiting the STAT3 and PI3K/AKT/mTOR signaling pathways. They also indicated that quercetin induced prosurvival autophagy in PEL cells [59].

5.9. Role in Apoptosis. In cellular organisms, one of the main causes of changes in cell morphology and eventually cell death is apoptosis or programmed cell death. This process generally occurs through two paths, intrinsic and extrinsic, both of which cause cell death by caspase proteins [124]. During apoptosis, changes occur on the cell surface, including bulging of the cell surface, cell shrinkage, fragmentation of the cell nucleus, chromatin condensation, and mRNA loss [112, 125]. Quercetin stimulates apoptosis through the mitochondrial pathway such as activation of caspase-3 and caspase-9 proteins, the release of cytochrome c, and cleavage of the PARP fragment (poly-ADP-ribose polymerase) [126, 127]. In a study on lymphoma cell lines (U937), quercetin and shHSP27 reduced the expression of proteins involved in the Notch/AKT/mTOR signaling pathway [128]. In another study on the Burji lymphoma cell line (Raji cell line), it was shown that 120 μM of quercetin increased the rate of cell apoptosis [16].

5.10. Therapeutic Potential of Quercetin for Lymphoma. Quercetin as an important polyphenolic bioflavonoid that exists in most fruits and vegetables [129] has antimalignant effects besides its antioxidant effects. Recently, some studies indicated that quercetin could suppress the proliferation of cancer cells in vitro [130–132]. Moreover, quercetin has different antimalignant activities against non-Hodgkin's lymphoma including a modulatory effect on the protein kinase (PKC) signaling pathway and apoptosis induction by inhibition of reactive oxygen species and tumor necrosis factor (TNF) receptor, suppression of the STAT3 pathway, and downregulation of Mcl-1, survivin, and p53 [81, 133, 134].

As mentioned above, it has been suggested that the mitochondria are the main targets for quercetin. The treatment with quercetin increased the release following TRAIL stimulation. Quercetin had synergic effects with TRAIL; however, the underlying molecular mechanism has not been identified [135]. The TRAIL-R2 stabilized in quercetin-mediated sensitization to TRAIL. Subsequently the expression of TRAIL-R2 at the cell surface upregulated and increased TRAIL DISC formation [136–138]. Since the mitochondrial apoptotic pathway is suppressed in resistant B-lymphoma cell lines, quercetin could restore the TRAIL apoptotic mechanism [80]. Quercetin-induced restoration of the mitochondrial apoptotic mechanism was correlated with Mcl-1 and survivin dysregulation. Survivin suppresses the mitochondrial Smac release, and it stabilizes XIAP which causes inhibition of caspase-9/3 activation at the postmitochondrial level [139]. Various transcription factors, e.g., signaling pathways such as p53 and AKT, negatively regulate the expression of survivin. In VAL and RL cells, the expression of survivin was inhibited following quercetin stimulation. Further studies are needed to clarify how the expression of survivin was inhibited by quercetin stimulation. Quercetin restores TRAIL-induced apoptosis in aggressive B-lymphoma cell lines via Mcl-1-induced proteasomal degradation. Mcl-1 preserves the cells from TRAIL-induced apoptosis by suppressing Bak, and Bid affects Bax activation. Moreover, quercetin-induced Mcl-1 proteasomal degradation was correlated with Mcl-1 ubiquitination and upregulation. Quercetin at higher concentrations

could induce apoptosis via downregulating Mcl-1 and activating Bax [140]. The advantages of quercetin including its low cost, potential beneficial effects, and its pharmacological safety suggest that quercetin could be a promising therapeutic approach for lymphoma.

5.11. Limitation of Quercetin Therapy. As mentioned earlier, the plant flavonoid quercetin has frequent biological and pharmacological functions. Numerous studies have shown that quercetin has anti-inflammatory, antioxidant, anticancer, antitoxic, and immunomodulatory properties. In addition to the beneficial and potential properties of quercetin in the treatment of diseases, their use has limitations that researchers need to pay close attention to. These limitations include poor solubility, low bioavailability, hydrophobic nature, and poor permeability. Many researchers are trying to overcome these limitations to use quercetin as a drug with minimal side effects and pharmacological limitations. For example, Nathiya et al. used polymer capsules to increase bioavailability and solubility by placing quercetin inside them [141]. Examining the pros and cons of quercetin in the brain and their diseases, Dajas et al. found that quercetin oxidation leads to the formation of quinones that are not reduced by antioxidants such as tocopherol (vitamin E) and ascorbate (vitamin C) and cause more damage to neurons (neurotoxicity). They concluded that modulating kinases could restore the redox equilibrium and was the only way to reduce quercetin restriction by preventing quinone formation [142]. In addition to these limitations, instability in physiological environments such as the stomach and intestines, a short half-life, and high metabolism in the liver before reaching the bloodstream reduces oral bioavailability. These factors limit the use of quercetin; to overcome these limitations, researchers have proposed efficient drug delivery systems that prevent drug damage to the gastrointestinal tract and reduce its instability when it enters the colon [143–145].

5.12. Clinical Studies with Quercetin. Previous studies have shown that quercetin has beneficial effects on many types of diseases. From recent years until now, the clinical (in vivo) use of quercetin in the treatment of various types of cancerous tumors has attracted the attention of many researchers. Several studies have shown that quercetin can exert its anticancer properties through different molecular mechanisms. It has been found that this compound with properties such as cell-cycle arrest, increased apoptosis, inhibition of angiogenesis and metastasis in vivo can help prevent the proliferation of tumor cells and reduce tumor size [146]. For example, in xenograft models of cancers such as leukemia and breast cancer, different doses of quercetin inhibit the cell cycle and increase programmed cell death by inhibiting the AKT/mTOR signaling pathway [147, 148]. In a study on prostate cancer, quercetin inhibited the growth of mouse prostate tumor cells in vivo by increasing the expression of Thrombospondin-1, an antiangiogenic factor [149]. The effect of quercetin on pulmonary-colorectal metastasis was also investigated, and it was found that a dose of 50 mg/kg of this compound reduces tumor metastasis [150]. Another study in BALB/c mice found that a dose of 150 mg/kg querce-

tin increased the apoptosis of liver tumor cells [151]. In a Phase I clinical trial, Ferry et al. examined the antiproliferative effect of quercetin on cisplatin-resistant ovarian cancer. Following treatment with 420 mg/m², in one patient the level of CA 125 decreased from 295 to 55 units/m²; in another patient, the level of serum alpha phytoprotein decreased. As a result, they found that i.v. quercetin inhibits tyrosine kinase activity in lymphocytes and ultimately has an antitumor effect [152]. As a result, due to the fact that quercetin has limited side effects and is well tolerated in humans, it can be used in vivo (clinical trial) to treat a variety of cancers. Unfortunately, clinical studies have not been used to treat lymphoma, so due to the high activity of researchers, it is hoped that this combination can be used to treat lymphoma.

6. Conclusion

Quercetin possesses antitumor effects on malignant cells and induces its anticancer effect against cancer cells via modulating various signaling pathways involved in cancer development and progression. Quercetin promotes apoptosis and autophagy by activating caspase-3 and inhibiting AKT, mTOR, and ERK phosphorylation in cancer cells. In addition, quercetin inhibits metastasis by downregulating VEGF and MMP. Quercetin targets mitochondria in cancer cells, decking the bioenergetics and triggering the intrinsic pathway of apoptosis. Quercetin could be helpful as a supplement in cancer prevention and as a low-toxicity therapeutic molecule for cancer treatment. It seems that quercetin can strengthen the effects of other chemotherapeutic drugs. However, more investigations are required to completely elucidate its fully exact mechanisms of action against lymphoid cancer. Taken together, quercetin may be a promising candidate for lymphoid cancer treatment especially in combination with other chemopreventive drugs due to its potential synergistic effects.

Disclosure

The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Conflicts of Interest

The authors declare that they have no competing interests.

Authors' Contributions

The conceptualization of this study came from S.R.S., V.T., P.A., W.C.C., and J.S.-R. They also coordinated the other authors and analyzed the collected papers. K.H., H.F., T.G., V.T., P.A., and J.S.-R. wrote the manuscript in collaboration with Ž.R. and W.C.C. Final editing was done by V.T. and J.S.-R. All authors have read and approved the manuscript. S.R.S. and K.H. contributed equally to this work.

Acknowledgments

We would like to thank Clinical Research Development Unit of Sina Educational, Research, and Treatment Center, Tabriz University of Medical Sciences, Tabriz, Iran, for their assistance in this study. Also, we thank Dr. Azita Dilmaghani for helpful advice. This work was supported and funded by Tabriz University of Medical Sciences (Grant number: 67959).

References

- [1] J. W. Breslin, Y. Yang, J. P. Scallan, R. S. Sweat, S. P. Adderley, and W. L. Murfee, "Lymphatic vessel network structure and physiology," *Comprehensive Physiology*, vol. 9, pp. 207–299, 2011.
- [2] A. Alitalo and M. Detmar, "Interaction of tumor cells and lymphatic vessels in cancer progression," *Oncogene*, vol. 31, no. 42, pp. 4499–4508, 2012.
- [3] R. Baskar, K. A. Lee, R. Yeo, and K. W. Yeoh, "Cancer and radiation therapy: current advances and future directions," *International Journal of Medical Sciences*, vol. 9, no. 3, pp. 193–199, 2012.
- [4] B. Valipour, A. Abedelahi, E. Naderali et al., "Cord blood stem cell derived CD16⁺ NK cells eradicated acute lymphoblastic leukemia cells using with anti-CD47 antibody," *Life Sciences*, vol. 242, p. 117223, 2020.
- [5] H. Wu, J. Xie, Q. Pan, B. Wang, D. Hu, and X. Hu, "Anticancer agent shikonin is an incompetent inducer of cancer drug resistance," *PLoS One*, vol. 8, no. 1, article e52706, 2013.
- [6] the International Natural Product Sciences Taskforce, A. G. Atanasov, S. B. Zotchev, V. M. Dirsch, and C. T. Supuran, "Natural products in drug discovery: advances and opportunities," *Nature Reviews Drug Discovery*, vol. 20, no. 3, pp. 200–216, 2021.
- [7] M. Schneckeburger, M. Dicato, and M. Diederich, "Plant-derived epigenetic modulators for cancer treatment and prevention," *Biotechnology Advances*, vol. 32, no. 6, pp. 1123–1132, 2014.
- [8] M. S. Butler, A. A. B. Robertson, and M. A. Cooper, "Natural product and natural product derived drugs in clinical trials," *Natural Product Reports*, vol. 31, no. 11, pp. 1612–1661, 2014.
- [9] M. Hashemzaei, A. K. Barani, M. Iranshahi et al., "Effects of resveratrol on carbon monoxide-induced cardiotoxicity in rats," *Environmental Toxicology and Pharmacology*, vol. 46, pp. 110–115, 2016.
- [10] M. Hashemzaei, R. Entezari Heravi, R. Rezaee, A. Roohbakhsh, and G. Karimi, "Regulation of autophagy by some natural products as a potential therapeutic strategy for cardiovascular disorders," *European Journal of Pharmacology*, vol. 802, pp. 44–51, 2017.
- [11] D. Nikitovic, A. M. Tsatsakis, N. K. Karamanos, and G. N. Tzanakakis, "The effects of genistein on the synthesis and distribution of glycosaminoglycans/proteoglycans by two osteosarcoma cell lines depends on tyrosine kinase and the estrogen receptor density," *Anticancer Research*, vol. 23, no. 1A, pp. 459–464, 2003.
- [12] M. Yamaguchi, T. Murata, B. A. S. S. E. L. F. el-Rayes, and M. Shoji, "The flavonoid p-hydroxycinnamic acid exhibits anticancer effects in human pancreatic cancer MIA PaCa-2 cells in vitro: comparison with gemcitabine," *Oncology Reports*, vol. 34, no. 6, pp. 3304–3310, 2015.
- [13] M. Cárdenas, M. Marder, V. C. Blank, and L. P. Roguin, "Antitumor activity of some natural flavonoids and synthetic derivatives on various human and murine cancer cell lines," *Bioorganic & Medicinal Chemistry*, vol. 14, no. 9, pp. 2966–2971, 2006.
- [14] F. L. Chan, H. L. Choi, Z. Y. Chen, P. S. F. Chan, and Y. Huang, "Induction of apoptosis in prostate cancer cell lines by a flavonoid, baicalin," *Cancer Letters*, vol. 160, no. 2, pp. 219–228, 2000.
- [15] S. Kawaii, Y. Tomono, E. Katase, K. Ogawa, and M. Yano, "Antiproliferative activity of flavonoids on several cancer cell lines," *Bioscience, Biotechnology, and Biochemistry*, vol. 63, no. 5, pp. 896–899, 1999.
- [16] M. Hashemzaei, A. D. Far, A. Yari et al., "Anticancer and apoptosis-inducing effects of quercetin in vitro and in vivo," *Oncology Reports*, vol. 38, no. 2, pp. 819–828, 2017.
- [17] Y. Li, J. Yao, C. Han et al., "Quercetin, inflammation and immunity," *Nutrients*, vol. 8, no. 3, p. 167, 2016.
- [18] I. Erlund, "Review of the flavonoids quercetin, hesperetin, and naringenin. Dietary sources, bioactivities, bioavailability, and epidemiology," *Nutrition Research*, vol. 24, no. 10, pp. 851–874, 2004.
- [19] J. Jakubowicz-Gil, R. Paduch, T. Piersiak, K. Głowniak, A. Gawron, and M. Kandefer-Szerszeń, "The effect of quercetin on pro-apoptotic activity of cisplatin in HeLa cells," *Biochemical Pharmacology*, vol. 69, no. 9, pp. 1343–1350, 2005.
- [20] S. Ramos, "Effects of dietary flavonoids on apoptotic pathways related to cancer chemoprevention," *The Journal of Nutritional Biochemistry*, vol. 18, no. 7, pp. 427–442, 2007.
- [21] M. A. Gates, A. F. Vitonis, S. S. Tworoger et al., "Flavonoid intake and ovarian cancer risk in a population-based case-control study," *International Journal of Cancer*, vol. 124, no. 8, pp. 1918–1925, 2009.
- [22] N. R. Song, M.-Y. Chung, N. J. Kang et al., "Quercetin suppresses invasion and migration of H-Ras-transformed MCF10A human epithelial cells by inhibiting phosphatidylinositol 3-kinase," *Food Chemistry*, vol. 142, pp. 66–71, 2014.
- [23] P. Baluk, J. Fuxe, H. Hashizume et al., "Functionally specialized junctions between endothelial cells of lymphatic vessels," *Journal of Experimental Medicine*, vol. 204, no. 10, pp. 2349–2362, 2007.
- [24] S. Arumugam, R. Sreedhar, R. A. Thandavarayan, V. Karuppagounder, and K. Watanabe, "Targeting fatty acid metabolism in heart failure: is it a suitable therapeutic approach?," *Drug Discovery Today*, vol. 21, no. 6, pp. 1003–1008, 2016.
- [25] A. E. Grulich, "Altered immunity as a risk factor for non-Hodgkin lymphoma," *Cancer Epidemiology, Biomarkers and Prevention*, vol. 16, no. 3, pp. 405–408, 2007.
- [26] C. F. Skibola, "Obesity, diet and risk of non-Hodgkin lymphoma," *Cancer Epidemiology, Biomarkers and Prevention*, vol. 16, no. 3, pp. 392–395, 2007.
- [27] J. R. Cerhan, A. Krick, O. Paltiel et al., "Medical history, lifestyle, family history, and occupational risk factors for diffuse large B-cell lymphoma: the interlymph non-Hodgkin lymphoma subtypes project," *Journal of the National Cancer Institute Monographs*, vol. 2014, no. 48, pp. 15–25, 2014.

- [28] M. Garcia, A. Jemal, E. Ward et al., *Global cancer facts & figures 2007*, vol. 1, American Cancer Society, Atlanta, GA, 2007.
- [29] B. Cady, "Regional lymph node metastases, a singular manifestation of the process of clinical metastases in cancer: contemporary animal research and clinical reports suggest unifying concepts," *Cancer Metastasis And The Lymphovascular System: Basis For Rational Therapy*, pp. 185–201, 2007.
- [30] B. Fisher, J.-H. Jeong, S. Anderson, J. Bryant, E. R. Fisher, and N. Wolmark, "Twenty-five-year follow-up of a randomized trial comparing radical mastectomy, total mastectomy, and total mastectomy followed by irradiation," *New England Journal of Medicine*, vol. 347, no. 8, pp. 567–575, 2002.
- [31] Early Breast Cancer Trialists' Collaborative Group (EBCTCG), "Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials," *The Lancet*, vol. 366, no. 9503, pp. 2087–2106, 2005.
- [32] C. B. Falkson, "How do I deal with the axilla in patients with a positive sentinel lymph node?," *Current Treatment Options in Oncology*, vol. 12, no. 4, pp. 389–402, 2011.
- [33] D. L. Morton, J. F. Thompson, A. J. Cochran et al., "Final trial report of sentinel-node biopsy versus nodal observation in melanoma," *New England Journal of Medicine*, vol. 370, no. 7, pp. 599–609, 2014.
- [34] T. P. Padera, E. F. J. Meijer, and L. L. Munn, "The lymphatic system in disease processes and cancer progression," *Annual Review of Biomedical Engineering*, vol. 18, no. 1, pp. 125–158, 2016.
- [35] S. Podgrabska and M. Skobe, "Role of lymphatic vasculature in regional and distant metastases," *Microvascular Research*, vol. 95, pp. 46–52, 2014.
- [36] T. Hoshida, N. Isaka, J. Hagendoorn et al., "Imaging steps of lymphatic metastasis reveals that vascular endothelial growth factor-C increases metastasis by increasing delivery of cancer cells to lymph nodes: therapeutic implications," *Cancer Research*, vol. 66, no. 16, pp. 8065–8075, 2006.
- [37] W. Zheng, A. Aspelund, and K. Alitalo, "Lymphangiogenic factors, mechanisms, and applications," *The Journal of Clinical Investigation*, vol. 124, no. 3, pp. 878–887, 2014.
- [38] T. P. Padera, A. H. Kuo, T. Hoshida et al., "Differential response of primary tumor versus lymphatic metastasis to VEGFR-2 and VEGFR-3 kinase inhibitors cediranib and vandetanib," *Molecular Cancer Therapeutics*, vol. 7, no. 8, pp. 2272–2279, 2008.
- [39] T. Karnezis, R. Shayan, C. Caesar et al., "VEGF-D promotes tumor metastasis by regulating prostaglandins produced by the collecting lymphatic endothelium," *Cancer Cell*, vol. 21, no. 2, pp. 181–195, 2012.
- [40] N. Roberts, B. Kloos, M. Cassella et al., "Inhibition of VEGFR-3 activation with the antagonistic antibody more potently suppresses lymph node and distant metastases than inactivation of VEGFR-2," *Cancer Research*, vol. 66, no. 5, pp. 2650–2657, 2006.
- [41] S. Srivastava, R. R. Somasagara, M. Hegde et al., "Quercetin, a natural flavonoid interacts with DNA, arrests cell cycle and causes tumor regression by activating mitochondrial pathway of apoptosis," *Scientific Reports*, vol. 6, no. 1, pp. 1–13, 2016.
- [42] W. Wätjen, G. Michels, B. Steffan et al., "Low concentrations of flavonoids are protective in rat H4IIE cells whereas high concentrations cause DNA damage and apoptosis," *The Journal of Nutrition*, vol. 135, no. 3, pp. 525–531, 2005.
- [43] M. Ezzati, B. Yousefi, K. Velaei, and A. Safa, "A review on anti-cancer properties of quercetin in breast cancer," *Life Sciences*, vol. 248, p. 117463, 2020.
- [44] J. Tan, B. Wang, and L. Zhu, "Regulation of survivin and Bcl-2 in HepG2 cell apoptosis induced by quercetin," *Chemistry & Biodiversity*, vol. 6, no. 7, pp. 1101–1110, 2009.
- [45] Q. Zhang, X. H. Zhao, and Z. J. Wang, "Flavones and flavonols exert cytotoxic effects on a human oesophageal adenocarcinoma cell line (OE33) by causing G2/M arrest and inducing apoptosis," *Food and Chemical Toxicology*, vol. 46, no. 6, pp. 2042–2053, 2008.
- [46] Q. Zhang, X. H. Zhao, and Z. J. Wang, "Cytotoxicity of flavones and flavonols to a human esophageal squamous cell carcinoma cell line (KYSE-510) by induction of G₂/M arrest and apoptosis," *Toxicology In Vitro*, vol. 23, no. 5, pp. 797–807, 2009.
- [47] W. P. Roos and B. Kaina, "DNA damage-induced cell death by apoptosis," *Trends in Molecular Medicine*, vol. 12, no. 9, pp. 440–450, 2006.
- [48] S.-K. Moon, G.-O. Cho, S.-Y. Jung et al., "Quercetin exerts multiple inhibitory effects on vascular smooth muscle cells: role of ERK1/2, cell-cycle regulation, and matrix metalloproteinase-9," *Biochemical and Biophysical Research Communications*, vol. 301, no. 4, pp. 1069–1078, 2003.
- [49] K. Gupta and D. Panda, "Perturbation of microtubule polymerization by quercetin through tubulin binding: a novel mechanism of its antiproliferative activity," *Biochemistry*, vol. 41, no. 43, pp. 13029–13038, 2002.
- [50] J. Á. F. Vara, E. Casado, J. de Castro, P. Cejas, C. Belda-Iniesta, and M. González-Barón, "PI3K/Akt signalling pathway and cancer," *Cancer Treatment Reviews*, vol. 30, no. 2, pp. 193–204, 2004.
- [51] N. Gulati, B. Laudet, V. M. Zohrabian, R. Murali, and M. Jhanwar-Uniyal, "The antiproliferative effect of quercetin in cancer cells is mediated via inhibition of the PI3K-Akt/PKB pathway," *Anticancer Research*, vol. 26, no. 2A, pp. 1177–1181, 2006.
- [52] S. Tanigawa, M. Fujii, and D.-X. Hou, "Stabilization of p53 is involved in quercetin-induced cell cycle arrest and apoptosis in HepG2 cells," *Bioscience, Biotechnology, and Biochemistry*, vol. 72, no. 3, pp. 797–804, 2008.
- [53] K. Polyak, Y. Xia, J. L. Zweier, K. W. Kinzler, and B. Vogelstein, "A model for p53-induced apoptosis," *Nature*, vol. 389, no. 6648, pp. 300–305, 1997.
- [54] K.-A. Yoon, Y. Nakamura, and H. Arakawa, "Identification of ALDH4 as a p53-inducible gene and its protective role in cellular stresses," *Journal of Human Genetics*, vol. 49, no. 3, pp. 134–140, 2004.
- [55] S. P. Hussain, P. Amstad, P. He et al., "p53-induced up-regulation of MnSOD and GPx but not catalase increases oxidative stress and apoptosis," *Cancer Research*, vol. 64, no. 7, pp. 2350–2356, 2004.
- [56] L. Gibellini, M. Pinti, M. Nasi et al., "Quercetin and cancer chemoprevention," *Evidence-based Complementary and Alternative Medicine*, vol. 2011, 15 pages, 2011.
- [57] D. Metodiewa, A. K. Jaiswal, N. Cenas, E. Dickanaité, and J. Segura-Aguilar, "Quercetin may act as a cytotoxic prooxidant after its metabolic activation to semiquinone and quinoidal product," *Free Radical Biology and Medicine*, vol. 26, no. 1-2, pp. 107–116, 1999.

- [58] H. M. Awad, M. G. Boersma, J. Vervoort, and I. M. C. M. Rietjens, "Peroxidase-Catalyzed Formation of Quercetin Quinone Methide-Glutathione Adducts," *Archives of Biochemistry and Biophysics*, vol. 378, no. 2, pp. 224–233, 2000.
- [59] M. Granato, C. Rizzello, M. S. Gilardini Montani et al., "Quercetin induces apoptosis and autophagy in primary effusion lymphoma cells by inhibiting PI3K/AKT/mTOR and STAT3 signaling pathways," *The Journal of Nutritional Biochemistry*, vol. 41, pp. 124–136, 2017.
- [60] M. Granato, C. Rizzello, M. A. Romeo et al., "Concomitant reduction of c-Myc expression and PI3K/AKT/mTOR signaling by quercetin induces a strong cytotoxic effect against Burkitt's lymphoma," *The International Journal of Biochemistry & Cell Biology*, vol. 79, pp. 393–400, 2016.
- [61] J. A. Flores-Pérez, F. de la Rosa Oliva, Y. Argenes, and A. Meneses-Garcia, "Nutrition, cancer and personalized medicine," *Translational Research and Onco-Omics Applications in the Era of Cancer Personal Genomics*, pp. 157–168, 2019.
- [62] T. L. Lee, J. Yeh, J. Friedman et al., "A signal network involving coactivated NF- κ B and STAT3 and altered p53 modulates BAX/BCL-XL expression and promotes cell survival of head and neck squamous cell carcinomas," *International Journal of Cancer*, vol. 122, no. 9, pp. 1987–1998, 2008.
- [63] L. Steelman, S. L. Abrams, J. Whelan et al., "Contributions of the Raf/MEK/ERK, PI3K/PTEN/Akt/mTOR and Jak/STAT pathways to leukemia," *Leukemia*, vol. 22, no. 4, pp. 686–707, 2008.
- [64] S. Borgés, E. Moudilou, C. Vouyovitch et al., "Involvement of a JAK/STAT pathway inhibitor: cytokine inducible SH2 containing protein in breast cancer," in *Hormonal Carcinogenesis V*, pp. 321–329, Springer, 2008.
- [65] L. T. Nguyen, Y. H. Lee, A. R. Sharma et al., "Quercetin induces apoptosis and cell cycle arrest in triple-negative breast cancer cells through modulation of Foxo3a activity," *The Korean Journal of Physiology & Pharmacology: Official Journal of the Korean Physiological Society and the Korean Society of Pharmacology*, vol. 21, no. 2, pp. 205–213, 2017.
- [66] C.-C. Chou, J. S. Yang, H. F. Lu et al., "Quercetin-mediated cell cycle arrest and apoptosis involving activation of a caspase cascade through the mitochondrial pathway in human breast cancer MCF-7 cells," *Archives of Pharmacal Research*, vol. 33, no. 8, pp. 1181–1191, 2010.
- [67] J.-Y. Zhang, M.-T. Lin, M.-J. Zhou et al., "Combinational treatment of curcumin and quercetin against gastric cancer MGC-803 cells in vitro," *Molecules*, vol. 20, no. 6, pp. 11524–11534, 2015.
- [68] R. Shafabakhsh and Z. Asemi, "Quercetin: a natural compound for ovarian cancer treatment," *Journal of Ovarian Research*, vol. 12, no. 1, pp. 55–59, 2019.
- [69] M. R. Indra, S. Karyono, R. Ratnawati, and S. G. Malik, "Quercetin suppresses inflammation by reducing ERK1/2 phosphorylation and NF kappa B activation in leptin-induced human umbilical vein endothelial cells (HUVECs)," *BMC Research Notes*, vol. 6, no. 1, pp. 1–8, 2013.
- [70] A. Wattel, S. Kamel, C. Prouillet et al., "Flavonoid quercetin decreases osteoclastic differentiation induced by RANKL via a mechanism involving NF κ B and AP-1," *Journal of Cellular Biochemistry*, vol. 92, no. 2, pp. 285–295, 2004.
- [71] E. J. Shin, J. S. Lee, S. Hong, T.-G. Lim, and S. Byun, "Quercetin directly targets JAK2 and PKC δ and prevents UV-induced photoaging in human skin," *International Journal of Molecular Sciences*, vol. 20, no. 21, p. 5262, 2019.
- [72] T. Chen, X. Zhang, G. Zhu et al., "Quercetin inhibits TNF- α induced HUVECs apoptosis and inflammation via downregulating NF- κ B and AP-1 signaling pathway in vitro," *Medicine*, vol. 99, no. 38, p. e22241, 2020.
- [73] S. Park, W. Lim, F. W. Bazer, K.-Y. Whang, and G. Song, "Quercetin inhibits proliferation of endometriosis regulating cyclin D1 and its target microRNAs in vitro and in vivo," *The Journal of Nutritional Biochemistry*, vol. 63, pp. 87–100, 2019.
- [74] A. B. Kunnumakkara, B. Shabnam, S. Girisa et al., "Inflammation, NF- κ B, and chronic diseases: how are they linked?," *Critical Reviews™ in Immunology*, vol. 40, no. 1, pp. 1–39, 2020.
- [75] Y. R. Puar, M. Shanmugam, L. Fan, F. Arfuso, G. Sethi, and V. Tergaonkar, "Evidence for the involvement of the master transcription factor NF- κ B in cancer initiation and progression," *Biomedicine*, vol. 6, no. 3, p. 82, 2018.
- [76] M. Reyes-Farias and C. Carrasco-Pozo, "The anti-cancer effect of quercetin: molecular implications in cancer metabolism," *International Journal of Molecular Sciences*, vol. 20, no. 13, p. 3177, 2019.
- [77] T.-J. Lee, O. H. Kim, Y. H. Kim et al., "Quercetin arrests G2/M phase and induces caspase-dependent cell death in U937 cells," *Cancer Letters*, vol. 240, no. 2, pp. 234–242, 2006.
- [78] T. Kawahara, N. Kawaguchi-Ihara, Y. Okuhashi, M. Itoh, N. Nara, and S. Tohda, "Cyclopamine and quercetin suppress the growth of leukemia and lymphoma cells," *Anticancer Research*, vol. 29, no. 11, pp. 4629–4632, 2009.
- [79] A. Fil'chenkov, M. Zavelevich, N. Khranovskaia, and V. Mykhailenko, "Apoptosis of human malignant lymphoid NAMALWA cells induced by resveratrol and quercetin," *Ukrains'kyi Biokhimichnyi Zhurnal (1999)*, vol. 78, pp. 112–119, 2006.
- [80] G. Jacquemin, V. Granci, A. S. Gallouet et al., "Quercetin-mediated Mcl-1 and survivin downregulation restores TRAIL-induced apoptosis in non-Hodgkin's lymphoma B cells," *Haematologica*, vol. 97, no. 1, pp. 38–46, 2012.
- [81] X. Li, X. Wang, M. Zhang, A. Li, Z. Sun, and Q. Yu, "Quercetin potentiates the antitumor activity of rituximab in diffuse large B-cell lymphoma by inhibiting STAT3 pathway," *Cell Biochemistry and Biophysics*, vol. 70, no. 2, pp. 1357–1362, 2014.
- [82] C. Salazar, O. Yañez, A. A. Elorza et al., "Biosystem analysis of the hypoxia inducible domain family member 2A: implications in cancer biology," *Genes*, vol. 11, no. 2, p. 206, 2020.
- [83] H. Okamoto, D. Yoshida, Y. Saito, and S. Mizusaki, "Inhibition of 12-O-tetradecanoylphorbol-13-acetate-induced ornithine decarboxylase activity in mouse epidermis by sweetening agents and related compounds," *Cancer Letters*, vol. 21, no. 1, pp. 29–35, 1983.
- [84] J. Y. Lim, J. Y. Lee, B. J. Byun, and S. H. Kim, "Fisetin targets phosphatidylinositol-3-kinase and induces apoptosis of human B lymphoma Raji cells," *Toxicology Reports*, vol. 2, pp. 984–989, 2015.
- [85] Y.-W. Xu, L. F. Zou, and F. Li, "Effect of quercetin on proliferation and apoptosis of multiple myeloma cells and its related mechanism," *Zhongguo Shi Yan Xue Ye Xue Za Zhi*, vol. 28, no. 4, pp. 1234–1239, 2020.
- [86] Y. Ma, Z. Jin, J. Huang et al., "Quercetin suppresses the proliferation of multiple myeloma cells by down-regulating IQ

- motif-containing GTPase activating protein 1 expression and extracellular signal-regulated kinase activation,” *Leukemia & Lymphoma*, vol. 55, no. 11, pp. 2597–2604, 2014.
- [87] A. K. Maurya and M. Vinayak, “Quercetin attenuates cell survival, inflammation, and angiogenesis via modulation of AKT signaling in murine T-cell lymphoma,” *Nutrition and Cancer*, vol. 69, no. 3, pp. 470–480, 2017.
- [88] A. K. Maurya and M. Vinayak, “PI-103 and quercetin attenuate PI3K-AKT signaling pathway in T-cell lymphoma exposed to hydrogen peroxide,” *PLoS One*, vol. 11, no. 8, article e0160686, 2016.
- [89] B. M. Cherry, N. Korde, M. Kwok, M. Roschewski, and O. Landgren, “Evolving therapeutic paradigms for multiple myeloma: back to the future,” *Leukemia & Lymphoma*, vol. 54, no. 3, pp. 451–463, 2013.
- [90] D. He, X. Guo, E. Zhang et al., “Quercetin induces cell apoptosis of myeloma and displays a synergistic effect with dexamethasone in vitro and in vivo xenograft models,” *Oncotarget*, vol. 7, no. 29, pp. 45489–45499, 2016.
- [91] A. Phan, R. Veldman, and M. J. Lechowicz, “T-cell lymphoma epidemiology: the known and unknown,” *Current Hematologic Malignancy Reports*, vol. 11, no. 6, pp. 492–503, 2016.
- [92] P. Ghione, A. J. Moskowitz, N. E. K. de Paola, S. M. Horwitz, and M. Ruella, “Novel immunotherapies for T cell lymphoma and leukemia,” *Current Hematologic Malignancy Reports*, vol. 13, no. 6, pp. 494–506, 2018.
- [93] S. M. Ansell, “Lymphoma,” *JAMA*, vol. 296, no. 19, pp. 2379–2384, 2006.
- [94] P. Mondello and G. S. Nowakowski, “Treatment of aggressive B cell lymphomas: updates in 2019,” *Current Hematologic Malignancy Reports*, vol. 15, no. 3, pp. 225–234, 2020.
- [95] K. Gatter and F. Pezzella, “Diffuse large B-cell lymphoma,” *Diagnostic Histopathology*, vol. 16, no. 2, pp. 69–81, 2010.
- [96] J. Higdon and J. Victoria, “Riboflavin. Micronutrient Information Center, Linus Pauling Institute, Oregon State University,” *Afr. J. Pharm. Pharmacol.*, vol. 2, pp. 29–36, 2007.
- [97] R. J. Williams, J. P. E. Spencer, and C. Rice-Evans, “Flavonoids: antioxidants or signalling molecules?,” *Free Radical Biology and Medicine*, vol. 36, no. 7, pp. 838–849, 2004.
- [98] W. M. Dabeek and M. V. Marra, “Dietary quercetin and kaempferol: bioavailability and potential cardiovascular-related bioactivity in humans,” *Nutrients*, vol. 11, no. 10, p. 2288, 2019.
- [99] C. L. Frankenfeld, J. R. Cerhan, W. Cozen et al., “Dietary flavonoid intake and non-Hodgkin lymphoma risk,” *The American Journal of Clinical Nutrition*, vol. 87, no. 5, pp. 1439–1445, 2008.
- [100] J. T. Yustein and C. V. Dang, “Biology and treatment of Burkitt’s lymphoma,” *Current Opinion in Hematology*, vol. 14, no. 4, pp. 375–381, 2007.
- [101] E. M. Molyneux, R. Rochford, B. Griffin et al., “Burkitt’s lymphoma,” *The Lancet*, vol. 379, no. 9822, pp. 1234–1244, 2012.
- [102] S. D. Dojcinov, F. Fend, and L. Quintanilla-Martinez, “EBV-positive lymphoproliferations of B-T- and NK-cell derivation in non-immunocompromised hosts,” *Pathogens*, vol. 7, no. 1, p. 28, 2018.
- [103] G. Brady, G. J. MacArthur, and P. J. Farrell, “Epstein-Barr virus and Burkitt lymphoma,” *Postgraduate Medical Journal*, vol. 84, no. 993, pp. 372–377, 2008.
- [104] R. Hoffman, E. J. Benz Jr., L. E. Silberstein, H. Heslop, J. Anastasi, and J. Weitz, *Hematology: Basic Principles and Practice*, Elsevier Health Sciences, 2013.
- [105] P. Karimi, B. M. Birmann, L. A. Anderson et al., “Risk factors for Burkitt lymphoma: a nested case-control study in the UK Clinical Practice Research Datalink,” *British Journal of Haematology*, vol. 181, no. 4, pp. 505–514, 2018.
- [106] H. Okamoto, D. Yoshida, and S. Mizusaki, “Inhibition of 12-O-tetradecanoylphorbol-13-acetate-induced induction in Epstein-Barr virus early antigen in Raji cells,” *Cancer Letters*, vol. 19, no. 1, pp. 47–53, 1983.
- [107] C. Carrasco-Pozo, K. N. Tan, M. Reyes-Farias et al., “The deleterious effect of cholesterol and protection by quercetin on mitochondrial bioenergetics of pancreatic β -cells, glycemic control and inflammation: In vitro and in vivo studies,” *Redox Biology*, vol. 9, pp. 229–243, 2016.
- [108] G. Carullo, A. R. Cappello, L. Frattaruolo, M. Badolato, B. Armentano, and F. Aiello, “Quercetin and derivatives: useful tools in inflammation and pain management,” *Future Medicinal Chemistry*, vol. 9, no. 1, pp. 79–93, 2017.
- [109] N. Jana, G. Břetislav, S. Pavel, and U. Pavla, “Potential of the flavonoid quercetin to prevent and treat cancer-current status of research,” *Klinicka Onkologie: Casopis Ceske a Slovenske Onkologicke Spolecnosti*, vol. 31, no. 3, pp. 184–190, 2018.
- [110] J.-H. Yang, T.-C. Hsia, H.-M. Kuo et al., “Inhibition of lung cancer cell growth by quercetin glucuronides via G2/M arrest and induction of apoptosis,” *Drug Metabolism and Disposition*, vol. 34, no. 2, pp. 296–304, 2006.
- [111] J.-A. Choi, J. Y. Kim, J. Y. Lee et al., “Induction of cell cycle arrest and apoptosis in human breast cancer cells by quercetin,” *International Journal of Oncology*, vol. 19, no. 4, pp. 837–844, 2001.
- [112] H. S. Tuli, S. S. Sandhu, and A. K. Sharma, “Pharmacological and therapeutic potential of Cordyceps with special reference to Cordycepin,” *3 Biotech*, vol. 4, no. 1, pp. 1–12, 2014.
- [113] G. Kumar, H. S. Tuli, S. Mittal, J. K. Shandilya, A. Tiwari, and S. S. Sandhu, “Isothiocyanates: a class of bioactive metabolites with chemopreventive potential,” *Tumor Biology*, vol. 36, no. 6, pp. 4005–4016, 2015.
- [114] P.-C. Kuo, H. F. Liu, and J. I. Chao, “Survivin and p53 Modulate Quercetin-induced Cell Growth Inhibition and Apoptosis in Human Lung Carcinoma Cells,” *Journal of Biological Chemistry*, vol. 279, no. 53, pp. 55875–55885, 2004.
- [115] C. Mu, P. Jia, Z. Yan, X. Liu, X. Li, and H. Liu, “Quercetin induces cell-cycle G1 arrest through elevating Cdk inhibitors p21 and p27 in human hepatoma cell line (HepG2),” *Methods and Findings in Experimental and Clinical Pharmacology*, vol. 29, no. 3, pp. 179–183, 2007.
- [116] J. H. Jeong, J. Y. An, Y. T. Kwon, J. G. Rhee, and Y. J. Lee, “Effects of low dose quercetin: cancer cell-specific inhibition of cell cycle progression,” *Journal of Cellular Biochemistry*, vol. 106, no. 1, pp. 73–82, 2009.
- [117] H. Sies, “Biochemistry of oxidative stress,” *Angewandte Chemie International Edition in English*, vol. 25, no. 12, pp. 1058–1071, 1986.
- [118] M. Kobori, Y. Takahashi, Y. Akimoto et al., “Chronic high intake of quercetin reduces oxidative stress and induces expression of the antioxidant enzymes in the liver and visceral adipose tissues in mice,” *Journal of Functional Foods*, vol. 15, pp. 551–560, 2015.

- [119] N. Koundouros and G. Pouligiannis, "Phosphoinositide 3-kinase/Akt signaling and redox metabolism in cancer," *Frontiers in Oncology*, vol. 8, p. 160, 2018.
- [120] D. J. Klionsky, "Autophagy revisited: a conversation with Christian de Duve," *Autophagy*, vol. 4, no. 6, pp. 740–743, 2008.
- [121] I. Tavassoly, *Dynamics of Cell Fate Decision Mediated by the Interplay of Autophagy and Apoptosis in Cancer Cells: Mathematical Modeling and Experimental Observations*, Springer, 2015.
- [122] Z. Wang, Q. Deng, Z. Wang, and T. Chong, "Effects of autophagy on the proliferation and apoptosis of clear cell renal carcinoma 786-O cells," *International Journal of Clinical and Experimental Pathology*, vol. 12, p. 1342, 2019.
- [123] C.-Y. Loh, A. Arya, A. F. Naema, W. F. Wong, G. Sethi, and C. Y. Looi, "Signal transducer and activator of transcription (STATs) proteins in cancer and inflammation: functions and therapeutic implication," *Frontiers in Oncology*, vol. 9, p. 48, 2019.
- [124] D. R. Green, *Means to an End: Apoptosis and Other Cell Death Mechanisms*, Cold Spring Harbor Laboratory Press, 2011.
- [125] D. Kashyap, H. S. Tuli, and A. K. Sharma, "Ursolic acid (UA): a metabolite with promising therapeutic potential," *Life Sciences*, vol. 146, pp. 201–213, 2016.
- [126] I.-K. Wang, S. Y. Lin-Shiau, and J. K. Lin, "Induction of apoptosis by apigenin and related flavonoids through cytochrome c release and activation of caspase-9 and caspase-3 in leukaemia HL-60 cells," *European Journal of Cancer*, vol. 35, no. 10, pp. 1517–1525, 1999.
- [127] M. Russo, R. Palumbo, I. Tedesco et al., "Quercetin and anti-CD95 (Fas/Apo1) enhance apoptosis in HPB-ALL cell line," *FEBS Letters*, vol. 462, no. 3, pp. 322–328, 1999.
- [128] X. Chen, X. S. Dong, H. Y. Gao et al., "Suppression of HSP27 increases the anti-tumor effects of quercetin in human leukemia U937 cells," *Molecular Medicine Reports*, vol. 13, no. 1, pp. 689–696, 2016.
- [129] H. Li, X. Zhao, Y. Ma, G. Zhai, L. Li, and H. Lou, "Enhancement of gastrointestinal absorption of quercetin by solid lipid nanoparticles," *Journal of Controlled Release*, vol. 133, no. 3, pp. 238–244, 2009.
- [130] J.-H. Moon, S. K. Eo, J. H. Lee, and S.-Y. Park, "Quercetin-induced autophagy flux enhances TRAIL-mediated tumor cell death," *Oncology Reports*, vol. 34, no. 1, pp. 375–381, 2015.
- [131] X. Gao, N. Huang, H. Shi et al., "Enhancing the anti-colon cancer activity of quercetin by self-assembled micelles," *International Journal of Nanomedicine*, vol. 10, p. 2051, 2015.
- [132] J. Lee, S.-I. Han, J.-H. Yun, and J. H. Kim, "Quercetin 3-O-glucoside suppresses epidermal growth factor-induced migration by inhibiting EGFR signaling in pancreatic cancer cells," *Tumor Biology*, vol. 36, no. 12, pp. 9385–9393, 2015.
- [133] A. K. Maurya and M. Vinayak, "Quercetin regresses Dalton's lymphoma growth via suppression of PI3K/AKT signaling leading to upregulation of p53 and decrease in energy metabolism," *Nutrition and Cancer*, vol. 67, no. 2, pp. 354–363, 2015.
- [134] A. K. Maurya and M. Vinayak, "Modulation of PKC signaling and induction of apoptosis through suppression of reactive oxygen species and tumor necrosis factor receptor 1 (TNFR1): key role of quercetin in cancer prevention," *Tumor Biology*, vol. 36, no. 11, pp. 8913–8924, 2015.
- [135] Y.-H. Jung, J. Heo, Y. J. Lee, T. K. Kwon, and Y.-H. Kim, "Quercetin enhances TRAIL-induced apoptosis in prostate cancer cells via increased protein stability of death receptor 5," *Life Sciences*, vol. 86, no. 9–10, pp. 351–357, 2010.
- [136] J. Y. Kim, E. H. Kim, S. S. Park, J. H. Lim, T. K. Kwon, and K. S. Choi, "Quercetin sensitizes human hepatoma cells to TRAIL-induced apoptosis via Sp1-mediated DR5 up-regulation and proteasome-mediated c-FLIPs down-regulation," *Journal of Cellular Biochemistry*, vol. 105, no. 6, pp. 1386–1398, 2008.
- [137] Y.-H. Kim, D. H. Lee, J. H. Jeong, Z. S. Guo, and Y. J. Lee, "Quercetin augments TRAIL-induced apoptotic death: involvement of the ERK signal transduction pathway," *Biochemical Pharmacology*, vol. 75, no. 10, pp. 1946–1958, 2008.
- [138] F. H. Psahoulia, K. G. Drosopoulos, L. Doubravka, L. Andera, and A. Pintzas, "Quercetin enhances TRAIL-mediated apoptosis in colon cancer cells by inducing the accumulation of death receptors in lipid rafts," *Molecular Cancer Therapeutics*, vol. 6, no. 9, pp. 2591–2599, 2007.
- [139] D. C. Altieri, "Survivin and IAP proteins in cell-death mechanisms," *Biochemical Journal*, vol. 430, no. 2, pp. 199–205, 2010.
- [140] G. Elia and M. G. Santoro, "Regulation of heat shock protein synthesis by quercetin in human erythroleukaemia cells," *Biochemical Journal*, vol. 300, no. 1, pp. 201–209, 1994.
- [141] S. Nathiya, M. Durga, and T. Devasena, "Quercetin, encapsulated quercetin and its application—a review," *Analgesia*, vol. 10, 2014.
- [142] F. Dajas, J. A. Abin-Carriquiry, F. Arredondo et al., "Quercetin in brain diseases: potential and limits," *Neurochemistry International*, vol. 89, pp. 140–148, 2015.
- [143] E. U. Graefe, J. Wittig, S. Mueller et al., "Pharmacokinetics and bioavailability of quercetin glycosides in humans," *The Journal of Clinical Pharmacology*, vol. 41, no. 5, pp. 492–499, 2001.
- [144] A. F. Almeida, G. I. A. Borge, M. Piskula et al., "Bioavailability of quercetin in humans with a focus on interindividual variation," *Comprehensive Reviews in Food Science and Food Safety*, vol. 17, no. 3, pp. 714–731, 2018.
- [145] P. Mukhopadhyay and A. K. Prajapati, "Quercetin in anti-diabetic research and strategies for improved quercetin bioavailability using polymer-based carriers—a review," *RSC Advances*, vol. 5, no. 118, pp. 97547–97562, 2015.
- [146] B. Salehi, L. Machin, L. Monzote et al., "Therapeutic potential of quercetin: new insights and perspectives for human health," *ACS Omega*, vol. 5, no. 20, pp. 11849–11872, 2020.
- [147] V. Maso, A. K. Calgarotto, G. C. Franchi Jr. et al., "Multitarget effects of quercetin in leukemia," *Cancer Prevention Research*, vol. 7, no. 12, pp. 1240–1250, 2014.
- [148] A. Rivera Rivera, L. Castillo-Pichardo, Y. Gerena, and S. Dharmawardhane, "Anti-breast cancer potential of quercetin via the Akt/AMPK/mammalian target of rapamycin (mTOR) signaling cascade," *PLoS One*, vol. 11, no. 6, article e0157251, 2016.
- [149] F. Yang, X. Jiang, L. Song et al., "Quercetin inhibits angiogenesis through thrombospondin-1 upregulation to antagonize human prostate cancer PC-3 cell growth in vitro and in vivo," *Oncology Reports*, vol. 35, no. 3, pp. 1602–1610, 2016.

- [150] J.-Y. Kee, Y. H. Han, D. S. Kim et al., "Inhibitory effect of quercetin on colorectal lung metastasis through inducing apoptosis, and suppression of metastatic ability," *Phytomedicine*, vol. 23, no. 13, pp. 1680–1690, 2016.
- [151] J. Zhou, L. Fang, J. Liao et al., "Investigation of the anti-cancer effect of quercetin on HepG2 cells in vivo," *PLoS One*, vol. 12, no. 3, article e0172838, 2017.
- [152] D. R. Ferry, A. Smith, J. Malkhandi et al., "Phase I clinical trial of the flavonoid quercetin: pharmacokinetics and evidence for in vivo tyrosine kinase inhibition," *Clinical Cancer Research*, vol. 2, no. 4, pp. 659–668, 1996.