*Minireview Article*

Therapeutic Potential of Traditional Chinese Medicine in Non-Hodgkin Lymphoma: A Comprehensive Review of Bioactive Compounds and Mechanisms of Action

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ABSTRACT

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| Non-Hodgkin lymphoma (NHL) is a heterogeneous group of hematologic malignancies with increasing global incidence and mortality. Despite advancements in conventional therapies, challenges remain due to treatment resistance, adverse effects, and disease relapse. Traditional Chinese Medicine (TCM) has been increasingly explored as an adjunctive and complementary approach in NHL treatment due to its multi-targeted, synergistic effects and holistic therapeutic principles. This review provides a comprehensive analysis of the potential applications of TCM in NHL, focusing on key bioactive compounds and their mechanisms of action.  Several TCM-derived compounds, including ginsenosides, triptolide, indirubin, rosmarinic acid, baicalin, wogonin, and icaritin, have demonstrated significant anti-lymphoma activities through mechanisms such as apoptosis induction, cell cycle arrest, immune modulation, and inhibition of oncogenic signaling pathways (e.g., PI3K/Akt/mTOR, NF-κB, and JAK/STAT). Medicinal fungi such as Coriolus versicolor have also shown promising immunomodulatory and anticancer effects, enhancing host immune responses against NHL. Preclinical and clinical studies suggest that TCM compounds can enhance the efficacy of conventional therapies, mitigate side effects, and improve patient outcomes.  While TCM holds promise for NHL management, further research is needed to validate its clinical efficacy, elucidate molecular interactions, and ensure safety in combination therapies. Future investigations should focus on rigorous clinical trials, pharmacokinetics, and mechanistic studies to establish evidence-based integration of TCM into NHL treatment paradigms. This review highlights the emerging role of TCM in hematological oncology and underscores its potential contribution to advancing therapeutic strategies for NHL. |

*Keywords: Non-Hodgkin Lymphoma, Traditional Chinese Medicine, Bioactive Compounds, Apoptosis, Immunotherapy, Molecular Mechanisms*

1. INTRODUCTION

Lymphoma, a cancer of the lymphatic system, originates from lymphoid cells. The World Health Organization (WHO) classification recognizes over 90 lymphoma subtypes. Based on the Revised European American Lymphoma (R.E.A.L) Classification developed by the International Lymphoma Study Group (ILSG) in the early 1990s, lymphomas are categorized as B-cell neoplasms, T-cell and Natural Killer cell neoplasms, and Hodgkin lymphoma. Clinically, lymphomas are classified as Hodgkin lymphomas (HLs) and non-Hodgkin lymphomas (NHLs), distinguished by the absence of Reed-Sternberg cells and distinct clinical presentations. According to the World Cancer Report, published by the International Agency for Research on Cancer, approximately 627,000 new lymphoma cases and 280,000 deaths occurred worldwide in 2020.

Non-Hodgkin Lymphoma (NHL) represents the most common hematological malignancy worldwide, encompassing more than 40 major subtypes and constituting the majority of lymphoma cases. World Health Organization data indicates approximately 540,000 new NHL cases occurred globally in 2020. The disease has demonstrated increasing incidence worldwide [1], with consistent rises observed across both sexes in North America, Europe, and East Asia since the 1970s [2-6].

While NHL can be diagnosed at any age, risk demonstrates strong correlation with advancing age, with over 50% of diagnoses occurring in patients aged 65 years or older [7]. The exact etiology remains undefined, though substantial evidence implicates viral infection [8], immunosuppression [9], and chronic antigenic stimulation [10] as contributing factors in certain cases.

Risk factors for NHL development can be categorized as non-modifiable (age, gender, race, family history, autoimmune disorders, immunosuppressive conditions, and genetic factors) and modifiable (ultraviolet radiation exposure, obesity, smoking and alcohol consumption, chemical exposure, and vitamin deficiency). The majority of NHL cases originate from B lymphocytes, with the remainder arising from NK cells or T lymphocytes [11]. Notably, approximately 30% of NHL patients present with primary extranodal lymphoma, showing varying frequency across different geographical regions [12, 13].

Clinical presentation of NHL encompasses diverse symptoms and signs corresponding to the site of origin. Common manifestations include lymphadenopathy, hepatosplenomegaly, fatigue, fever, weight loss, and location-specific symptoms. However, many patients, particularly those with indolent subtypes, may remain asymptomatic.

Diffuse large B-cell lymphoma, an aggressive B-cell subtype, represents the most prevalent form of NHL, accounting for approximately 30% of adult cases [14]. Among indolent NHLs, follicular lymphoma comprises approximately 22% of cases [14], while all other NHL subtypes demonstrate frequencies below 10% [15]. GLOBOCAN data indicates NHL represents 2.8% of all cancer diagnoses, with gender-specific incidence rates of 6.0/100,000 in males and 4.1/100,000 in females [16].

Global estimates indicate approximately 248,700 deaths due to NHL worldwide, representing 2.6% of all cancer mortality [14]. Despite advances in understanding disease pathophysiology, mortality rates remained relatively stable [17]. Global NHL mortality rates showed minimal change, from 3.19 per 100,000 population in 1990 to 3.18 per 100,000 in 2017 [17].

Mortality rates demonstrate significant variation across countries with different Human Development Index (HDI) classifications. According to GLOBOCAN 2018, mortality rates in high HDI nations reached 3.2/100,000 for men, while low/medium HDI nations reported rates of 2.0/100,000 and 1.9/100,000 for women, respectively [18]. Mortality demonstrates strong age correlation, peaking in individuals over 85 years [19], reflecting both increased incidence and decreased survival in elderly populations.

Gender disparities in mortality are pronounced, with men experiencing approximately double the mortality rate of women. In the European Union, mortality rates were 4.1/100,000 in men and 2.5/100,000 in women [20]. United States data revealed rates of 5.1/100,000 and 4.1/100,000 for men and women, respectively [14]. Similar patterns were observed in Japan, with rates of 3.7/100,000 among men and 1.99/100,000 among women [20]. Most countries have demonstrated increasing mortality trends over recent decades, followed by a gradual declining trend in recent years [20-22].

NHL survival varies significantly by subtype, stage, and geographical location. Five-year survival rates reach approximately 70% in the United States but only 38% in China [19]. The International Prognostic Index, widely accepted as the primary prognostic model, identifies several independent survival factors: age, Ann Arbor stage, serum lactate dehydrogenase concentration, Eastern Cooperative Oncology Group performance status, and number of extranodal sites [23]. Additional factors, including cigarette smoking, alcohol consumption, and obesity, have demonstrated adverse impacts on survival [24-26].

Treatment approaches typically combine radiotherapy and chemotherapy, with specific protocols determined by histologic type, stage, and other clinical factors. Additional therapeutic options include immunotherapy, targeted drug therapy, stem cell transplantation, and surgery. While chemotherapy remains the primary treatment modality for most NHL patients, often combined with immunotherapy, a "watch and wait" strategy may be appropriate for indolent NHL cases, even in advanced-stage disease [27].

Radiation therapy plays a crucial role in low-grade NHL management and serves multiple purposes: symptom palliation, localized disease treatment, central nervous system prophylaxis, intracranial metastases management, and tumor mass reduction in advanced stages [28]. While chemotherapy represents the primary therapeutic modality for aggressive NHL subtypes [28, 29], its efficacy is limited in indolent lymphomas [29], leading to the adoption of monoclonal therapy and radiation as standard care [28].

Targeted therapy offers precise identification and attack of cancer cells, though the presence of target substances on healthy cells can lead to various adverse effects. Recent advances in immunotherapy have introduced multiple novel approaches, including monoclonal antibodies, immune checkpoint inhibitors, non-specific immunotherapy, oncolytic virus therapy, T-cell therapy, and cancer vaccines. These therapeutic strategies enhance anticancer activity through immune cell stimulation [30], and may extend patient survival. However, widespread implementation faces significant barriers, including prohibitive costs and toxicity profiles [31]. Additionally, comparative efficacy studies between immunotherapy and conventional treatment approaches remain incomplete.

Current NHL research encompasses multiple therapeutic fronts, including the development of novel chemotherapy agents, monoclonal antibodies, and alternative strategies such as antisense oligonucleotides. Despite significant therapeutic advances, substantial challenges persist, particularly drug resistance and toxicity, which continue to impact patient survival and mortality rates. These ongoing challenges underscore the urgent need for novel, effective therapeutic agents. Natural products derived from fungi, plants, and microorganisms have historically served as foundational sources for traditional medicine, including Traditional Chinese Medicine (TCM). With millennia of development and distinctive theoretical foundations, TCM has emerged as a prominent complementary and alternative medicine approach, recognized for its potential therapeutic applications in cancer treatment [32]. The fundamental principles of TCM emphasize syndrome differentiation and holistic intervention [33].

TCM regimens demonstrate therapeutic efficacy through their multi-component, multi-target characteristics [24], typically incorporating multiple constituents that produce synergistic effects through simultaneous interaction with diverse molecular targets [25]. A notable example is YIV-906 (formerly PHY906, KD018), a preparation combining Scutellaria baicalensis Georgi, Glycyrrhiza uralensis Fisch, Paeonia lactiflora Pall, and Ziziphus jujuba Mill, which has demonstrated efficacy as adjuvant therapy in multiple cancer clinical trials [26, 33]. Similarly, vincristine, derived from Catharanthus roseus leaves, exhibits significant anticancer activity across various cancer types [34].

While numerous natural compounds demonstrate anti-tumor activity, research specifically addressing TCM applications in NHL remains limited. This review examines the experimental evidence supporting TCM efficacy in NHL treatment and provides framework for future therapeutic investigations.

2.1 Ginseng: Therapeutic Applications and Anticancer Properties

Ginseng, particularly Panax ginseng and Panax quinquefolius, has been explored for its potential benefits in cancer treatment, including NHL. The herb is primarily recognized for its ability to alleviate cancer-related fatigue and may also have direct anticancer effects. Panax ginseng C.A.Mey (Araliaceae family), traditionally utilized throughout Asia [35], contains diverse bioactive compounds including glucosides, alkaloids, polysaccharides, and ginsenosides [36]. Among these constituents, ginsenosides, classified as tetracyclic triterpene saponins, are considered the primary pharmacologically active components [37, 38]. These compounds are categorized into two main groups: protopanaxadiol and protopanaxatriol [38]. The qualitative and quantitative composition of ginsenosides demonstrates significant variation influenced by multiple factors, including species, plant age, environmental conditions, harvesting period, and preservation methodology [39, 40].

Historically recognized as an energy-promoting tonic herb [35], ginseng demonstrates multiple biological activities including anti-aging, neuroregulation, and immunomodulation. Experimental studies utilizing cell culture and animal models have established its anticancer effects through various mechanisms, particularly angiogenesis inhibition and apoptosis induction [36, 41]. Investigation across multiple cancer cell lines has demonstrated broad-spectrum anticancer potential. Additionally, ginseng exhibits significant immunomodulatory properties through enhancement of lymphocyte proliferation and activity, inflammation suppression, and cytokine production modulation [42].

Korean Red Ginseng water extract has demonstrated significant anticancer efficacy in murine xenograft lymphoma models. Its mechanisms of action encompass tumor growth suppression, angiogenesis inhibition, apoptosis induction, immune function enhancement, and reduction of inflammation, oxidative stress, and metastatic potential [43, 44].

Saponins, particularly ginsenosides, represent extensively studied components for their therapeutic potential in cancer treatment through immune cell regulation. Both preclinical and clinical investigations have yielded promising results for various ginseng-derived saponins, including G-Rh1, G-F2, G-Rg3, G-Rp1, and component K [45, 46]. Steamed ginseng-leaf components, specifically ginsenosides Rh3 and Rk2, demonstrate enhanced chemotherapy potentiation and proliferation inhibition in human leukemia HL-60 cells through cell cycle arrest and apoptosis induction [47, 48].

Ginsan, an acidic polysaccharide derived from Panax ginseng, shows particular promise in cancer therapy through its immunomodulatory effects. This compound promotes T helper 1 cell and macrophage differentiation, enhances cytokine secretion, and stimulates lymphokine-activated killer cell generation in conjunction with recombinant interleukin-2 [49]. These immunological effects position Ginsan as a promising candidate for cancer immunotherapy applications.

Table 1 Bioactive Compounds Isolated from Ginseng: Cellular Targets, Mechanisms of Action, and Therapeutic Effects

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Compound | Target Cells | Mechanism of Action | Therapeutic Effects | Reference |
| Ginsan | T helper 1 (Th1) cells and macrophages | Promotes Th1 and macrophage differentiation; Enhances cytokine secretion; Stimulates lymphokine-activated killer (LAK) cell generation synergistically with rIL-2 | Contributes to cancer immunoprevention and immunotherapy | Kim, K.H., et al.[49] |
| Ginsenosides | Lymphocytes | Enhances lymphocyte proliferation and activity; Suppresses inflammation; Modulates cytokine production | Regulates lymphocyte proliferation and immune function | Cho, J.Y., et al.[42] |
| Korean Red Ginseng water extract | Lymphoma cells | Inhibits tumor growth and angiogenesis; Induces apoptosis; Enhances immune function; Suppresses inflammation and oxidative stress | Suppresses xenografted lymphoma cell growth | Park, J.G., et al.[43] |
| Panax ginseng | Cancer cells | Induces apoptosis; Inhibits angiogenesis and metastasis; Enhances immune function | Contributes to cancer control; Reduces fatigue and debility | Chang, Y.S., et al.[50] |
| Panax ginseng | Immune cells | Increases immune cell population and activity; Enhances cytokine production; Reduces inflammation | Functions as immunomodulator with NK cell activation properties | Kim, J.Y., et al.[51] |
| Siberian ginseng Extract | Cancer cells | Activates NK cells; Stimulates splenocyte proliferation; Enhances macrophage activity and cytokine production | Inhibits cancer cell proliferation | Cichello, S.A., et al.[52] |
| Steamed ginseng-leaf components | Cancer cells | Potentiates chemotherapy efficacy; Induces cell cycle arrest and apoptosis | Demonstrates enhanced cytotoxicity against HL-60 leukemia cells | Tung, N.H., et al.[47] |
| Korean Red Ginseng-derived fractions | Cancer cells | Induces apoptosis; Activates immune cells | Suppresses tumor growth | Baek, K.S., et al.[44] |
| Ginsengenin derivatives | Cancer cells | Inhibits HIF-1 pathway involved in tumor growth, angiogenesis, and metastasis | Suppresses HeLa cell proliferation, migration, and invasion; Promotes apoptosis | Guo, H.Y., et al.[53] |

2.2 Triptolide: Molecular Mechanisms and Therapeutic Applications

Triptolide, a bioactive compound isolated from Tripterygium wilfordii Hook f., has emerged as a promising anticancer agent through extensive research investigations. This natural compound demonstrates significant antitumor activity through diverse molecular mechanisms, establishing its potential role in cancer therapeutics.

Recent studies have elucidated multiple mechanisms of action. Huang et al. demonstrated triptolide's inhibitory effects on T-cell lymphoblastic lymphoma cell viability, invasion, and epithelial-mesenchymal transition through PI3K-AKT-mTOR pathway regulation [50]. Synergistic effects were observed by Hua et al., who reported enhanced apoptotic induction when triptolide was combined with arsenic trioxide in SKM-1 human myelodysplastic syndrome cells [51]. Additionally, triptolide demonstrates inhibitory effects on lymph node metastasis in non-Hodgkin lymphoma through SDF-1/CXCR4 axis modulation [52].

Molecular investigations have revealed triptolide's ability to inhibit ADAM10 (a disintegrin and metalloproteinase 10) expression in cancer cells, contributing to its antitumor efficacy [53]. This mechanism is particularly significant given ADAM10's established role in cancer cell invasion and metastatic processes.

Triptolide also demonstrates significant antiviral properties in oncological contexts. Studies have shown its ability to decrease latency-associated nuclear antigen 1 expression and reduce viral titers in Kaposi's sarcoma-associated herpesvirus-related primary effusion lymphoma cells [54]. Furthermore, triptolide inhibits Epstein-Barr virus-positive B lymphocyte proliferation through LMP1 viral protein downregulation [55].

Additional therapeutic applications include chemosensitization, with studies demonstrating triptolide's ability to enhance multiple myeloma cell sensitivity to dexamethasone through microRNA modulation [56]. Cytotoxic effects have been observed across multiple cell lines, including human promyelocytic leukemia, T cell lymphoma, and hepatocellular carcinoma [57]. Mechanistic studies have revealed triptolide's role in inducing mitochondria-mediated apoptosis in Burkitt's lymphoma cells through SIRT3 expression enhancement and GSK-3β deacetylation [58].

Recent investigations have focused on triptolide's effects on telomerase activity, a critical factor in cancer cell proliferation. Studies demonstrate its inhibitory effects on human telomerase reverse transcriptase through downregulation of translation factors SP1 and c-Myc in Epstein-Barr virus-positive B lymphocytes [59]. Additional research has shown triptolide's ability to inhibit hTERT transcription through transcription factor specificity protein 1 downregulation in primary effusion lymphoma cells [60].

**Table 2 Molecular Mechanisms and Signaling Pathways of Triptolide in Various Target Cells**

| Target Cell | Mechanism of Action | Signaling Pathway | Reference |
| --- | --- | --- | --- |
| T-cell lymphoblastic lymphoma | Inhibition of cell viability, invasion, and epithelial-mesenchymal transition | PI3K-AKT-mTOR pathway | Huang, Y., et al.[54] |
| SKM-1 human myelodysplastic syndrome | Apoptosis induction | Not determined | Hua, H.Y., et al.[55] |
| Non-Hodgkin lymphoma | Lymph node metastasis inhibition | SDF-1/CXCR4 axis | Zhang, C., et al.[56] |
| Cancer cells | ADAM10 expression inhibition | Not determined | Soundararajan, R., et al. [57] |
| Kaposi's sarcoma-associated herpesvirus-related primary effusion lymphoma | Reduction of latency-associated nuclear antigen 1 expression and viral titers | Not determined | Huang, X., et al.[58] |
| Multiple myeloma cells | Enhancement of dexamethasone sensitivity | microRNA-mediated | Huang, X., et al.[60] |
| Promyelocytic leukemia, T cell lymphoma, and hepatocellular carcinoma | Cytotoxicity induction | Not determined | Chan, E.W., et al.[61] |
| Burkitt's lymphoma | Mitochondria-mediated apoptosis induction | SIRT3 upregulation and GSK-3β deacetylation | Kong, J., et al.[62] |
| Epstein-Barr virus-positive B lymphocytes | Telomerase reverse transcriptase inhibition via SP1 and c-Myc downregulation | Not determined | Long, C., et al.[63] |
| Epstein-Barr virus-positive B lymphocytes | Proliferation inhibition through LMP1 viral protein downregulation | Not determined | Zhou, H., et al.[59] |
| Primary effusion lymphoma | hTERT transcription inhibition through specificity protein 1 downregulation | Not determined | Long, C., et al.[64] |

2.3 Indigo Naturalis: Therapeutic Applications in Hematological Malignancies

Indigo Naturalis, a traditional Chinese medicine with centuries of documented use in inflammatory and immune-related disorders, has demonstrated significant pharmacological effects through its bioactive compounds in recent investigations. Dihydroxyquingdainone, a principal active constituent of Indigo Naturalis, exhibits apoptotic activity in leukemia and lymphoma cells through Bcl-2 and caspase-3-dependent mechanisms [61]. Another key compound, indirubin, demonstrates synergistic effects with arsenic disulfide in human diffuse large B-cell lymphoma cells [62]. This synergistic relationship holds particular clinical significance as it potentially allows dose reduction of arsenic disulfide, thereby minimizing toxicity risks while maintaining therapeutic efficacy.

Arsenic disulfide is a drug that has been used for the treatment of leukemia. However, it has several side effects, and enhancing its efficacy can reduce the required dosage, thereby minimizing the risk of toxicity. Indirubin has been shown to enhance the efficacy of arsenic disulfide and can be a helpful adjunct in the treatment of leukemia.

Indirubin derivatives, particularly indirubin-3'-monoxime, demonstrate significant antiproliferative effects against malignant lymphoid cells [63], and induce cell death through reactive oxygen species (ROS) generation [64]. This compound exhibits dose-dependent growth inhibition across multiple tumor cell lines, primarily through G2/M phase cell cycle arrest, with efficacy varying by cell line characteristics [65-67].

The mechanism of indirubin-3'-monoxime's antiproliferative effects on human lymphocytes involves both direct and indirect pathways. Direct inhibition occurs through competitive ATP binding in cyclin-dependent-kinase catalytic domains, while indirect effects manifest through transcriptional and translational gene expression regulation [68-70]. As a novel AHR ligand, indirubin-3-monoxime demonstrates immunotoxic properties, evidenced by increased CYP1A and COX-2 protein expression in U937 cells and potential modulation of indoleamine 2,3-dioxygenase expression [71].

Research has established that cutaneous T-cell lymphoma cells are susceptible to ROS-induced targeting, activating extrinsic apoptosis through downregulation of cellular FLICE-inhibitory protein and X-linked inhibitor of apoptosis protein - a pathway efficiently activated by indirubin derivatives [64].

Meisoindigo, another Indigo Naturalis derivative, demonstrates multiple anticancer mechanisms: induction of marked apoptosis, G0/G1 phase cell cycle arrest, human telomerase reverse transcriptase downregulation, and enhancement of conventional chemotherapeutic agent efficacy (cytarabine and idarubicin). This compound shows particular promise in acute myeloid leukemia treatment through antiproliferative and cytotoxic effects [72].

The combination of indirubin and meisoindigo has demonstrated clinical efficacy in chronic myelogenous leukemia (CML) treatment in China. Despite incomplete understanding of their precise mechanisms, this combination induces hematologic remission in chronic phase CML patients with efficacy comparable to hydroxyurea and busulfan [73].

**Table 3. Active Compounds Extracted from Indigo, Their Target Cells, and Mechanisms**

| Main Active Compound | Target Cell | Mechanism of Action | Reference |
| --- | --- | --- | --- |
| Dihydroxyquingdainone | Leukaemia and Lymphoma Cells | Induces Apoptosis | Baas, J., et al.[65] |
| Indirubin | Human diffuse large B-cell lymphoma cells | Enhances arsenic disulfide-induced apoptosis | Wang, L., et al.[66] |
| Indirubin derivatives | Malignant lymphoid cells; Cutaneous T-cell lymphoma cells | Inhibits proliferation; Induces cell death via reactive oxygen species | Chebel, A., et al.[67] |
| Indirubin-3-monoxime | Normal lymphocytes | Multifactorial inhibition of proliferation | Soltan, M.Y., et al.[68] |
| Meisoindigo | Human acute myeloid leukemia cells | Inhibits proliferation and induces cell death | Kagialis-Girard, S., et al.[74] |

2.4 Garcinia: Novel Therapeutic Applications in Hematological Malignancies

The genus Garcinia, comprising various tropical plant species, has emerged as a significant source of potential anticancer compounds. Recent investigations have elucidated multiple bioactive constituents with therapeutic potential across various malignancies. Studies examining Garcinia morella have demonstrated its capacity to induce apoptotic cell death in T-Cell Murine Lymphoma [74]. Similarly, forbesione, isolated from Garcinia hanburyi, exhibits significant antitumor effects against cholangiocarcinoma both in vitro and in vivo [75].

Gambogic acid, another notable Garcinia-derived compound, demonstrates potent apoptosis-inducing properties in diffuse large B-cell lymphoma cells [76]. Additionally, investigations have identified viral SUMO2-interaction inhibitors from Garcinia species that show promise in primary effusion lymphoma treatment [77].

α-Mangostin, extracted from Garcinia mangostana, demonstrates significant anticancer activity against chronic myeloid leukemia cells, with enhanced efficacy through autophagy inhibition [78]. α-Mangostin, extracted from Garcinia mangostana, demonstrates significant anticancer activity against chronic myeloid leukemia cells, with enhanced efficacy through autophagy inhibition [79].

These findings collectively highlight the therapeutic potential of Garcinia-derived compounds in hematological malignancies and support further investigation of their molecular mechanisms and clinical applications.

**Table 4. Active Compounds Extracted from Garcinia, and Their Target Cells, Mechanisms, and Pathways**

| Main Active Compound | Target Cell | Mechanism of Action | Pathway | Reference |
| --- | --- | --- | --- | --- |
| Garcinia morella | T-Cell Murine Lymphoma | Apoptotic Induction | Unknown | Choudhury, B., et al.[78] |
| Forbesione | Cholangiocarcinoma | Inhibition of growth | Synergistic effect with 5-Fluorouracil | Boueroy, P., et al.[79, 83] |
| Gambogic acid | Diffuse large B-cell lymphoma cells | Inducing proteasome inhibition | Unknown | Shi, X., et al.[80] |
| α-mangostin | Chronic myeloid leukemia cells | Augmenting anticancer activity | Inhibition of autophagy | Chen, J.J., et al.[82] |

2.5 Prunella vulgaris: Clinical Applications and Antineoplastic Properties

Prunella vulgaris L. represents a perennial herb with established therapeutic applications in Traditional Chinese Medicine spanning several centuries. Its conventional applications encompass various conditions, including inflammatory disorders, pyrexia, and hypertension. Recent clinical evidence documents sustained complete remission in a patient with double-hit diffuse large B-cell lymphoma following treatment with integrated chemoimmunotherapy and Chinese herbal medicine incorporating P. vulgaris [80].

Recent studies have shown that the extract of this plant has potential anti-tumor effects. The active compounds in Prunella vulgaris include flavonoids, phenolic acids, triterpenoids, and polysaccharides. Among them, rosmarinic acid (RA), a phenolic acid, has been identified as the major active compound responsible for the plant's pharmacological activities. RA has been shown to inhibit cancer cell proliferation in multiple studies. It can reduce cell viability, slow cell cycle progression, and halt cancer cell growth [81-84]. These effects could potentially help suppress the uncontrolled growth of lymphoma cells. One of the key mechanisms by which RA exerts its anticancer effects is by promoting apoptosis in cancer cells. RA has been observed to induce apoptosis in cancer cells by upregulating pro-apoptotic proteins such as p53, Bax, Fas, Bad, caspase-3, and caspase-9, and downregulating anti-apoptotic proteins including Bcl-2, Mcl, and Bcl-xl [85]. RA could also affect oxidative stress in cancer cells by inhibiting the intracellular generation of reactive oxygen species [85], and modulating antioxidant enzymes, potentially protecting against oxidative damage [84]. Additionally, RA exhibits anti-inflammatory properties by inhibiting NF-κB activity, and reducing the production of prostaglandin E2 (PGE2), nitric oxide (NO), and cyclooxygenase-2 [83]. RA has been shown to inhibit cancer cell migration and invasion by decreasing the expression of invasion-related factors [86], and suppressing the expression of adhesion molecules like ICAM-1 and VCAM-1 [83]. While these mechanisms represent potential pathways through which rosmarinic acid might exert anticancer effects in lymphoma cells. RA treatment has been observed to increase the ratio of pro-apoptotic proteins (e.g., Bax) to anti-apoptotic proteins (e.g., Bcl-2) [82, 83], and activate caspase-3 and caspase-9, which are crucial enzymes in the apoptotic process [81, 82]. RA has also demonstrated the ability to reduce cancer cell migration and invasion [81], which are important factors in cancer metastasis. RA has been shown to inhibit the ADAM17/EGFR/AKT/GSK3β axis, which the pathway is involved in progression of various types of cancer, including some lymphomas [81, 84]. Studies have demonstrated that RA can suppress the PI3K/AKT/mTOR pathway, which is known to promote cell survival and proliferation [82, 84]. This pathway is often overactive in lymphomas and is a target for some current therapies. RA has been found to inhibit NF-κB activity, which is crucial for inflammation and cancer progression, particularly important in many types of lymphoma [82-84]. Research has indicated that RA may enhance the sensitivity of cancer cells to chemotherapy drugs. For instance, RA co-treatment increased the inhibitory effect of cisplatin on cancer cell viability [81]. This suggests that RA could potentially be used as an adjuvant therapy to improve the efficacy of standard lymphoma treatments. RA has demonstrated the ability to reduce cancer cell migration, invasion, and angiogenesis. For non-Hodgkin lymphoma, this could mean limiting the growth of new blood vessels necessary for tumor development [82], and reducing the expression of angiogenic and inflammatory factors like IL-1β, TNF-α, and TGF-β [82]. RA's strong antioxidant and anti-inflammatory properties may contribute to its anticancer effects in non-Hodgkin lymphoma by reducing oxidative stress and inflammation, which are known to contribute to cancer progression [82], and inhibiting the production of pro-inflammatory factors like IL-6, IL-1β, and TNF-α [83]. Research suggests that RA may enhance the sensitivity of cancer cells to chemotherapy drugs. For non-Hodgkin lymphoma treatment, this could mean potentially serving as an effective adjuvant treatment with chemotherapy for non-Hodgkin's lymphoma [85].

A study examined the inhibitory effect of Spica prunellae extract (SPE), derived from Prunella vulgaris, on T lymphoma cell EL-4 tumor. The results showed that the extract exhibited significant anti-tumor activity by inducing apoptosis of the tumor cells. The study suggested that the SPE could be a potential therapeutic agent for the treatment of T lymphoma [87]. Research has also demonstrated its potential efficacy and safety as both a standalone treatment and as an adjuvant to chemotherapy for NHL patients [80, 85]. Spica prunellae contains several bioactive compounds, including triterpenoic acids, ursolic acid, and caffeic acid, that contribute to its anti-cancer properties [85]. These components have shown cytotoxic effects against various cancer cell lines, including leukemia and lymphoma cells. SPE promotes apoptosis in lymphoma cells by increasing expression of Bcl-2 protein, decreasing expression of Bax protein [80], and upregulating microRNA-34a (miR-34a), which downregulates Notch1, Notch2, and Bcl-2 [88]. The SPE could also suppresses lymphoma cell growth by inhibiting c-Myc and CDK6 oncogenes [80]. SPE could affects multiple signaling pathways including HIF-1, estrogen, NOD-like receptors, PI3K-Akt, and TNF [89], showing the signaling pathway modulation effects to cancer cells. SPE also exhibits antioxidant properties that may contribute to its anti-cancer effects [90]. Another study found that when SPE was combined with paclitaxel, it enhanced the inhibition of lymphoma Raji cell proliferation by tenfold [90], moreover, a randomized clinical trial involving 101 NHL patients demonstrated the effectiveness of SPE, showed a promising results for SPE as a treatment for NHL [85].

Another study showed a purified substance from Prunella vulgaris var. lilacina, 2a,3a-dihydroxyurs-12-en-28-oic acid (DHURS), a pentacyclic triterpenoid, has shown various pharmacological activities, including anticancer effects [91]. DHURS could induce apoptotic DNA fragmentation of human acute leukemia Jurkat T cells via loss of mitochondrial membrane potential, mitochondrial cytochrome c release into cytoplasm, activation of caspase-3, -7, -8, and -9, and resultant cleavage of PARP [92, 93], demonstrating potential effectiveness against a hematological malignancy. DHURS-induced apoptosis was negatively regulated by overexpression of Bcl-2 [93]. DHURS triggers apoptosis in cancer cells through multiple pathways, not only by caspase cascade activation, mitochondrial pathway, and through the Bcl-2 family regulation, which downregulates anti-apoptotic Bcl-2 protein, and upregulates pro-apoptotic Bax protein [94].

**Table 5. Potential Anticancer Compounds from Prunella vulgaris and Mechanisms of Action and Affected Pathways in Various Cancer Cell Types**

| Main Active Compound | Target Cell | Mechanism of Action | Pathway | Reference |
| --- | --- | --- | --- | --- |
| Rosmarinic acid (RA) | Various cancer cells, including lymphoma cells | - Inhibits cancer cell proliferation  - Promotes apoptosis  - Reduces oxidative stress  - Anti-inflammatory properties  - Inhibits cancer cell migration and invasion  - Enhances sensitivity to chemotherapy drugs | - Upregulates pro-apoptotic proteins (p53, Bax, Fas, Bad, caspase-3, caspase-9)  - Downregulates anti-apoptotic proteins (Bcl-2, Mcl, Bcl-xl)  - Inhibits NF-κB activity - Reduces prostaglandin E2, nitric oxide, and cyclooxygenase-2 production  - Inhibits ADAM17/EGFR/AKT/GSK3β axis  - Suppresses PI3K/AKT/mTOR pathway | Huang, Sirajudeen, Azhar, Kowalczyk, Huang, et al. [85-90] |
| Spica prunellae extract (SPE) | T lymphoma cell EL-4 tumor, lymphoma Raji cells | - Induces apoptosis  - Suppresses lymphoma cell growth  - Enhances inhibition of lymphoma cell proliferation when combined with paclitaxel | - Increases expression of Bcl-2 protein  - Decreases expression of Bax protein  - Upregulates microRNA-34a (miR-34a), which downregulates Notch1, Notch2, and Bcl-2  - Inhibits c-Myc and CDK6 oncogenes  - Modulates HIF-1, estrogen, NOD-like receptors, PI3K-Akt, and TNF pathways | Liang,Huang, Mao, Fang, XH, Mak,et al.[84, 89, 91-94] |
| 2a,3a-dihydroxyurs-12-en-28-oic acid (DHURS) | Human acute leukemia Jurkat T cells | - Induces apoptotic DNA fragmentation - Triggers apoptosis through multiple pathways | - Loss of mitochondrial membrane potential  - Mitochondrial cytochrome c release into cytoplasm - Activation of caspase-3, -7, -8, and -9  - Cleavage of PARP - Negatively regulated by overexpression of Bcl-2  - Downregulates anti-apoptotic Bcl-2 protein  - Upregulates pro-apoptotic Bax protein | Ma, Reyes, Woo, Wang, et al.[95-98] |

2.6 Scutellaria Baicalensis: Anticancer Effects and Therapeutic Potential

Scutellaria baicalensis, commonly known as Chinese skullcap, demonstrates significant anticancer potential against lymphoma and leukemia. Studies have shown that extracts from this herb exhibit anti-proliferative and apoptotic effects on acute lymphocytic leukemia, lymphoma, and myeloma cell lines [95, 96]. The herb contains several active compounds including baicalin, baicalein, wogonin, and scutellarin, which contribute to its therapeutic effects.

Scutellarin, a flavonoid glucuronide, has shown inhibitory effects on human Burkitt lymphoma Namalwa cells by inducing apoptosis and inhibiting cell proliferation [99]. These effects are mediated through various signaling pathways including PI3K-Akt, Jak/STAT, ERK/AMPK, and Wnt/β-catenin [99, 100]. Additionally, scutellarin suppresses proliferation and promotes apoptosis in A549 lung adenocarcinoma cells via the AKT/mTOR/4EBP1 and STAT3 pathways [101].

Baicalein, another major flavonoid from S. baicalensis, induces cell death in T cell lymphoma cells by inhibiting the thioredoxin system [102-104]. It also suppresses proliferation in acute T-lymphoblastic leukemia Jurkat cells through modulation of the Wnt/β-catenin signaling pathway [102-104].

Baicalin has demonstrated apoptosis-inducing effects in Burkitt lymphoma CA46 cells by regulating the expression of Bcl-2, Bax, caspase-3, and caspase-9 [105]. Studies have also shown that baicalin induces apoptosis in lymphocytic leukemia, lymphoma, and myeloma cells through modulation of the Bcl family and mitochondrial damage [95, 106-108].

Wogonin exerts cytotoxic effects on Raji cells (Burkitt's lymphoma) through the LMP1/miR-155/NF-κB/PU.1 pathway [109]. In mantle cell lymphoma cells, wogonin induces G0/G1 phase arrest and apoptosis via the NF-κB/cyclin D1 and NF-κB/Bcl-2/caspase pathways [110]. Additionally, wogonin inhibits CDK9, leading to downregulation of Mcl-1 and induction of apoptosis in B-cell lymphoma [111, 112]. Notably, wogonin shows selective apoptosis induction in THP-1 human monocytic leukemia cells [95].

**Table 6. Active Compounds of Scutellaria baicalensis and Their Therapeutic Mechanisms**

| Main Active Compound | Target Cell | Mechanism of Action | Pathway | Reference |
| --- | --- | --- | --- | --- |
| Scutellarin | Human Burkitt lymphoma Namalwa cells | Cell proliferation inhibition and apoptosis induction | PI3K-Akt signaling pathway, Jak/STAT, ERK/AMPK, Wnt/β-catenin | Feng, Vesaghhamedani, et al.[103,104] |
| Scutellarin | A549 lung adenocarcinoma cells | Proliferation suppression and apoptosis promotion | AKT/mTOR/4EBP1 and STAT3 pathways | Cao, P., et al.[105] |
| Baicalein | T cell lymphoma cells | Cell death induction | Thioredoxin system inhibition | Wang, R., et al. [112] |
| Baicalein | Acute T-lymphoblastic leukemia Jurkat cells | Proliferation suppression | Wnt/β-catenin signaling pathway | Wang, R., et al. [112] |
| Baicalin | Burkitt lymphoma CA46 cells | Apoptosis induction | Bcl-2, Bax, caspase-3, and caspase-9 regulation | Huang, Y., et al. [109] |
| Baicalin | Lymphocytic leukemia, lymphoma, and myeloma cells | Apoptosis induction | Bcl family modulation, mitochondrial damage | Kumagai, T., et al. [99] |
| Wogonin | Raji cells (Burkitt's lymphoma) | Cytotoxic effects | LMP1/miR-155/NF-κB/PU.1 pathway | Wu, X., et al. [113] |
| Wogonin | Mantle cell lymphoma cells | G0/G1 phase arrest and apoptosis | NF-κB/cyclin D1 and NF-κB/Bcl-2/caspase pathways | Xu, P.P., et al. [114] |
| Wogonin | B-cell lymphoma | Apoptosis induction | CDK9 inhibition, Mcl-1 downregulation | Polier, Wu, et al. [115,116] |
| Wogonin | THP-1 human monocytic leukemia cells | Selective apoptosis induction | Not specified in source | Kumagai, T., et al. [99] |

2.7 Icaritin: Natural Compound with Promising Antineoplastic Potential

Icaritin, a prenylflavonoid derivative isolated from Epimedium brevicornum, demonstrates broad-spectrum antitumor activities. Contemporary research elucidated its cytotoxic effect and underlying mechanisms in inducing apoptosis in human Burkitt lymphoma cell, PC12 cells, and extranodal NKT-cell lymphoma [113-115]. Icaritin demonstrated cytotoxic effects on Burkitt lymphoma cell lines (Raji and P3HR-1), inhibiting proliferation and inducing apoptosis through mechanisms such as S-phase arrest, caspase activation, and modulation of apoptotic proteins (e.g., reducing Bcl-2 and c-Myc levels while increasing Bax expression). These findings suggest its potential for broader application in hematopoietic malignancies, including NHL [113].

Icaritin exerts its antitumor effects through multiple pathways, such as activation of caspase-8 and caspase-9, cleavage of PARP, and modulation of Bcl-2/Bax ratios [113]. Icaritin could enhance CD8+ T-cell activity, reduce immunosuppressive myeloid-derived suppressor cells (MDSCs), and downregulate inflammatory pathways like IL-6/JAK2/STAT3 and TLR-MyD88-NFκB. Icaritin also suppresses oncogenic pathways such as MAPK and PI3K-Akt [116, 117].

In Burkitt lymphoma cells, icaritin has been found to induce apoptosis via the PI3K/Akt pathway by downregulating Bcl-2 expression and upregulating Bax expression, leading to the release of cytochrome c from mitochondria and subsequent activation of the caspase cascade [113]. In PC12 cells, icariin, the glycoside form of icaritin, has been shown to attenuate autophagy induced by oxygen-glucose deprivation/reperfusion (OGD/R) via a Bcl-2-dependent crosstalk between apoptosis and autophagy [114]. In extranodal NKT-cell lymphoma, icaritin has been reported to induce lytic cytotoxicity via the JAK/STAT pathway by activating NK cells and upregulating perforin and granzyme B expression [115]. Furthermore, icaritin has also been found to regulate the expression of various proteins involved in cell proliferation and survival, including cyclin D1, p21, p53, and c-Myc [118]. These findings suggest that icaritin has a broad spectrum of anti-tumor activity and may be a promising natural candidate for hematological malignancies therapy.

**Table 7. Potential Anticancer Activitys from Icaritin, and Mechanisms of Action and Affected Pathways in Various Cancer Cell Types**

| Main Active Compound | Target Cell | Mechanism of Action | Pathway | Reference |
| --- | --- | --- | --- | --- |
| Icaritin | Burkitt lymphoma cell lines (Raji and P3HR-1) | Inhibits proliferation and induces apoptosis through S-phase arrest, caspase activation, and modulation of apoptotic proteins (e.g., reducing Bcl-2 and c-Myc levels) | PI3K/Akt pathway by downregulating Bcl-2 expression and upregulating Bax | Li, Z.J., et al., [117] |
| Icariin | PC12 cells | Attenuates autophagy induced by oxygen-glucose deprivation/reperfusion (OGD/R) | Bcl-2-dependent crosstalk between apoptosis and autophagy | Mo, Z.T., et al. [118] |
| Icaritin | Extranodal NKT-cell lymphoma | Induces lytic cytotoxicity by activating NK cells and upregulating perforin and granzyme B expression | JAK/STAT pathway | Wu, T., et al. [119] |
| Icaritin | Various cancer cells | Regulates the expression of proteins involved in cell proliferation and survival, including cyclin D1, p21, p53, and c-Myc | Multiple pathways, including caspase activation, MAPK, and PI3K-Akt | Li, Liu, Xue, Yang, et al.[117, 120-122] |

2.8 Coriolus Versicolor: Bioactive Medicinal Mushroom with Immunomodulatory and Antitumor Potential

Coriolus versicolor, also known as Yunzhi, is a type of mushroom that has shown potential for use in the treatment of cancer. It possesses both anti-tumor and immunopotentiating activities. One study has shown C. versicolor extract could have effect on cytokine production and stimulate proliferation of murine splenic lymphocytes in vitro [119]. Coriolus versicolor is a medicinal mushroom widely studied for its polysaccharides [120-122], particularly PSK (polysaccharide-Krestin) and PSP (polysaccharopeptide), which are composed of β-glucan macromolecules bound to peptides, contributing to their biological activity [120, 121, 123, 124]. One study has also demonstrated that the extract of Coriolus versicolor inhibited the growth of human leukemia xenografts and induced apoptosis through the mitochondrial pathway [125]. Additionally, the extract has also been found to induce apoptosis in human leukemia and lymphoma cells [126].

PSK, an aqueous extract from the mycelium of Coriolus versicolor, exhibits direct inhibitory effects on cancer cell growth and induces apoptosis of the Burkitt lymphoma cell [120, 127]. PSK has also been found to reduce superoxide radicals in the tumor microenvironment, restoring immune cell functionality [128, 129]. Additionally PSK could activate NK cells and increase their cytotoxicity. It also enhances IFN-γ production in NK cells when combined with accessory cell-derived cytokines like IL-12 and IL-18, and stimulates TNF-α secretion through TLR2 or TLR4-dependent pathways [130-133]. Other compounds extracted from C. versicolor, such as beta-glucans [134], dectin-1 [135], have been shown to activate NK cells and stimulate production of interferon-gamma and tumor necrosis factor [134, 135].

**Table 8. Potential Anticancer Compounds from Coriolus versicolor, and Mechanisms of Action and Affected Pathways in Various Cancer Cell Types**

| Main Active Compound | Target Cell | Mechanism of Action | Pathway | Reference |
| --- | --- | --- | --- | --- |
| C. versicolor extract | Murine splenic lymphocytes | Stimulates cytokine production and proliferation of lymphocytes in vitro | Not specified | Ho, C.Y., et al. [123] |
| C. versicolor extract | Human leukemia and lymphoma cells | Induces apoptosis | Not specified | Lau, C.B., et al. [130] |
| PSK | Human leukemia xenografts, Burkkit lymphoma cells | Inhibits cancer cell growth, induces apoptosis, reduces superoxide radicals in tumor microenvironment, restores immune cell functionality | Mitochondrial pathway, TLR2 or TLR4-dependent pathways | Habtemariam, Ho, Hattori, Saleh, Vannucci, et al. [124, 129, 131-133] |
| PSK | Natural killer (NK) cells | Activates NK cells, increases cytotoxicity, enhances IFN-γ production when combined with IL-12 and IL-18, stimulates TNF-α secretion | TLR2 or TLR4-dependent pathways | Quayle, Lu, Wenner, Price, et al. [134-137] |
| PSP | Not specified | Exhibits biological activity due to β-glucan macromolecules bound to peptides | Not specified | Habtemariam, He, Dou, Chang, et al.[124, 125, 127, 128] |
| Beta-glucans | Natural killer (NK) cells | Activates NK cells, stimulates production of interferon-gamma and tumor necrosis factor | Not specified | Kang, S.C., et al.[138] |
| Dectin-1 | Natural killer (NK) cells | Activates NK cells, stimulates production of interferon-gamma and tumor necrosis factor | Not specified | Taylor, P.R., et al. [139] |

3. Conclusion

Non-Hodgkin's lymphoma (NHL) treatment has seen significant advancements in recent years, with options such as chemotherapy, biological therapy, and radiotherapy, either alone or in combination. However, despite these advances, the side effects associated with NHL treatment remain challenging for patients to tolerate. Additionally, the relapse rate for NHL patients undergoing treatment is relatively high. These factors emphasize the necessity for ongoing research and development to enhance the effectiveness of NHL treatment while reducing its negative effects.

Traditional Chinese Medicine (TCM) is a therapeutic method with unique characteristics. It has been reported to be used as an adjuvant therapy for cancer treatment. Preliminary studies suggest that combining TCM with chemotherapy may improve objective response rates and disease control rates compared to chemotherapy alone. Additionally, it could decrease side effects in patients treated with chemotherapy or radiotherapy.

In this review, we discuss various TCM herbs, their active compounds, and the potential mechanisms and pathways involved in their experimental use for treating cancer. The aim is to explore the potential benefits of TCM for cancer patients.

Further research is needed to evaluate the effectiveness and safety of Traditional Chinese Medicine modalities in cancer treatment. In particular, future investigations should prioritize outcome measures that assess the impact of TCM interventions on patients' quality of life. Such research can help to establish TCM as a viable and effective treatment option for cancer patients.

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