*Minireview Article*

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

.

ABSTRACT

|  |
| --- |
| 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 from ginseng, triptolide from Tripterygium wilfordii, indirubin from Indigo naturalis, rosmarinic acid from Prunella vulgaris, baicalin and wogonin from Scutellaria baicalensis, icaritin from Epimedium brevicornum, and polysaccharides from Coriolus versicolor, have demonstrated significant anti-lymphoma activities through mechanisms such as apoptosis induction, cell cycle arrest, immune modulation, and inhibition of oncogenic signaling pathways. 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. |

*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].

In the Indian subcontinent, NHL presents unique epidemiological patterns that differ from Western populations. India reports an age-adjusted incidence rate of approximately 2.5-3.0 per 100,000 population, with notable variations across different regions [154]. The disease demonstrates a younger age distribution compared to Western countries, with median age at diagnosis being 45-50 years versus 65 years in developed nations [7]. Extranodal presentations are particularly common in the Indian subcontinent, accounting for approximately 40-45% of cases, with gastrointestinal and bone marrow involvement being frequent sites [155-157]. T-cell lymphomas constitute a higher proportion of NHL cases in this region, representing nearly 25-30% of diagnoses compared to 10-15% in Western populations [154]. The burden of NHL in India has been increasing, with projected annual increases of 3-4% in incidence rates, largely attributed to improved diagnostic capabilities, increasing life expectancy, and changing lifestyle factors [154].

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[136].

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 histo-pathology 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 [137]. 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 [138]. 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 [139,140]. Despite significant therapeutic advances, substantial challenges persist, particularly drug resistance and toxicity, which continue to impact patient survival and mortality rates [141,142]. 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) [143-148]. 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 | Huang, Y., 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 | Hua, H.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 | Zhang, C., 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 | Soundararajan, R., 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 | Long, C., et al. [54] |
| SKM-1 human myelodysplastic syndrome | Apoptosis induction | Not determined | Zhou, H., et al.[55] |
| Non-Hodgkin lymphoma | Lymph node metastasis inhibition | SDF-1/CXCR4 axis | Huang, X., et al.[56] |
| Cancer cells | ADAM10 expression inhibition | Not determined | Chan, E.W., 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 | Kong, J., et al.[58] |
| Multiple myeloma cells | Enhancement of dexamethasone sensitivity | microRNA-mediated | Long, C., et al.[60] |
| Promyelocytic leukemia, T cell lymphoma, and hepatocellular carcinoma | Cytotoxicity induction | Not determined | Baas, J., et al.[61] |
| Burkitt's lymphoma | Mitochondria-mediated apoptosis induction | SIRT3 upregulation and GSK-3β deacetylation | Wang, L., et al.[62] |
| Epstein-Barr virus-positive B lymphocytes | Telomerase reverse transcriptase inhibition via SP1 and c-Myc downregulation | Not determined | Chebel, A., et al.[63] |
| Epstein-Barr virus-positive B lymphocytes | Proliferation inhibition through LMP1 viral protein downregulation | Not determined | Long, C., et al.[59] |
| Primary effusion lymphoma | hTERT transcription inhibition through specificity protein 1 downregulation | Not determined | Soltan, M.Y., 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 [149-151]. 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 [152, 153]. 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 | Marko, D., et al.[65] |
| Indirubin | Human diffuse large B-cell lymphoma cells | Enhances arsenic disulfide-induced apoptosis | Hoessel, R., et al.[66] |
| Indirubin derivatives | Malignant lymphoid cells; Cutaneous T-cell lymphoma cells | Inhibits proliferation; Induces cell death via reactive oxygen species | Damiens, E., et al.[67] |
| Indirubin-3-monoxime | Normal lymphocytes | Multifactorial inhibition of proliferation | Knockaert, M., et al.[68] |
| Meisoindigo | Human acute myeloid leukemia cells | Inhibits proliferation and induces cell death | Choudhury, B., 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 | Chen, J.J., et al.[78] |
| Forbesione | Cholangiocarcinoma | Inhibition of growth | Synergistic effect with 5-Fluorouracil | Boueroy, P., Azhar, M.K., et al.[79, 83] |
| Gambogic acid | Diffuse large B-cell lymphoma cells | Inducing proteasome inhibition | Unknown | Liang, H., et al.[80] |
| α-mangostin | Chronic myeloid leukemia cells | Augmenting anticancer activity | Inhibition of autophagy | Sirajudeen, F., 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, M., Liu, Y., Mao, X., Fang, Y., XH, W., Mak, W.C.K., 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 | Kowalczyk, A., XH, Ma, Reyes, Woo, Wang, 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 | Kumagai, Tao, Ye, 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 | Verma, Rahmani, et al.[103,104] |
| Scutellarin | A549 lung adenocarcinoma cells | Proliferation suppression and apoptosis promotion | AKT/mTOR/4EBP1 and STAT3 pathways | Huang, Y., et al.[105] |
| Baicalein | T cell lymphoma cells | Cell death induction | Thioredoxin system inhibition | Wu, X., et al. [112] |
| Baicalein | Acute T-lymphoblastic leukemia Jurkat cells | Proliferation suppression | Wnt/β-catenin signaling pathway | Wu, X., et al. [112] |
| Baicalin | Burkitt lymphoma CA46 cells | Apoptosis induction | Bcl-2, Bax, caspase-3, and caspase-9 regulation | Wu, X., et al. [109] |
| Baicalin | Lymphocytic leukemia, lymphoma, and myeloma cells | Apoptosis induction | Bcl family modulation, mitochondrial damage | Feng, Y., et al. [99] |
| Wogonin | Raji cells (Burkitt's lymphoma) | Cytotoxic effects | LMP1/miR-155/NF-κB/PU.1 pathway | Li, Z.J., 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 | Mo, Z.T., et al. [114] |
| Wogonin | B-cell lymphoma | Apoptosis induction | CDK9 inhibition, Mcl-1 downregulation | Wu, Liu, et al., [115,116] |
| Wogonin | THP-1 human monocytic leukemia cells | Selective apoptosis induction | Not specified in source | Feng, Y., 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 | Xue, Z., et al., [117] |
| Icariin | PC12 cells | Attenuates autophagy induced by oxygen-glucose deprivation/reperfusion (OGD/R) | Bcl-2-dependent crosstalk between apoptosis and autophagy | Yang, X.J., 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 | Ho, C.Y., 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 | Xue, Habtemariam, He, Ng, 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 | Dou, H., et al. [123] |
| C. versicolor extract | Human leukemia and lymphoma cells | Induces apoptosis | Not specified | Quayle, K., 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 | Chang, Vannucci, Lu, Wenner, Price, 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 | Kang, Taylor, Freedman AS, Du, et al. [134-137] |
| PSP | Not specified | Exhibits biological activity due to β-glucan macromolecules bound to peptides | Not specified | Chang, Ho, Hattori, Saleh, 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 | Ghemrawi, R., et al.[138] |
| Dectin-1 | Natural killer (NK) cells | Activates NK cells, stimulates production of interferon-gamma and tumor necrosis factor | Not specified | Suresh, T., et al. [139] |

3. Discussion

Traditional Chinese Medicine practitioners have long recognized that cancer formation represents a manifestation of imbalanced yin-yang and deficient vital energy with pathogenic excess within the body. The herbal formulations transmitted by generations of medical practitioners demonstrate sophisticated strategies for treating malignancies that ingeniously address various aspects of what modern medicine terms "cancer hallmarks [158]," reflecting the profound and flexible principles of Traditional Chinese Medicine, and its potential for synergistic therapeutic applications.

Different formulations regulate cancer cell growth and death through distinct yet complementary mechanisms, including cell cycle control (such as G0/G1 phase arrest by ginsenosides, S phase arrest by triptolide, and G2/M phase arrest by indirubin derivatives) and apoptosis induction (such as icaritin and baicalin activating intrinsic mitochondrial pathways, rosmarinic acid activating both intrinsic and extrinsic apoptotic pathways, and triptolide overcoming apoptotic resistance). The excellence of Chinese medicine extends beyond direct attack on tumors to encompass holistic regulation that strengthens vital energy to enhance the body's anti-cancer capacity through immune modulation (such as ginsan enhancing Th1 cells, Coriolus versicolor polysaccharides activating NK cells, and PSK and PSP initiating TLR pathways), cutting off nutritional supply routes through anti-angiogenic effects (such as ginsenosides inhibiting VEGF and rosmarinic acid suppressing angiogenic factors including IL-1β, TNF-α, and TGF-β), and preventing metastatic spread through anti-metastatic mechanisms (such as triptolide regulating SDF-1/CXCR4 axis, rosmarinic acid inhibiting ADAM17/EGFR pathways, and icaritin downregulating inflammatory pathways like IL-6/JAK2/STAT3).

From this perspective, Chinese medicine's approach to cancer treatment does not rely on isolated interventions but employs comprehensive strategies of multiple methods and compound formulations, embodying the wisdom of "monarch, minister, assistant, and guide" principles [159]. The mechanistic diversity observed among TCM compounds suggests significant potential for synergistic combinations that could address multiple cancer hallmarks simultaneously, positioning Traditional Chinese Medicine as an important adjunctive approach in treating malignancies such as non-Hodgkin lymphoma through its multi-targeted characteristics and synergistic effects.

The multi-targeted nature of individual TCM compounds, combined with their potential for synergistic interactions, establishes Traditional Chinese Medicine as a valuable adjunctive approach in NHL management. The ability to simultaneously address multiple cancer hallmarks through relatively non-toxic natural compounds presents opportunities for improving therapeutic outcomes while potentially reducing the adverse effects associated with conventional single-target therapies. However, rigorous clinical trials are essential to validate these mechanistic insights and establish optimal dosing and combination protocols for clinical implementation.

4. 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 represents a therapeutic approach with distinctive characteristics that has been increasingly investigated as adjuvant therapy for cancer treatment. Preliminary clinical studies suggest that combining TCM with conventional chemotherapy may improve objective response rates and disease control rates compared to chemotherapy alone. Additionally, TCM interventions could potentially decrease adverse effects in patients receiving chemotherapy or radiotherapy treatments. The active compounds discussed in this review demonstrate multiple mechanisms of action that target fundamental cancer hallmarks, suggesting potential for synergistic therapeutic applications. Future clinical investigations should prioritize standardized outcome measures that comprehensively assess the impact of TCM interventions on patients' quality of life, progression-free survival, and overall therapeutic response to establish evidence-based integration protocols.

In this review, we have examined various TCM herbs, their active compounds, and the potential mechanisms and pathways involved in their experimental use for treating cancer, with the aim of exploring the potential benefits of TCM for cancer patients. While the majority of studies examined in this review demonstrate promising anticancer activities in cancer cell lineage models, it is important to acknowledge that results may vary considerably when implemented in human physiological systems. The translation from in vitro findings to clinical applications requires careful consideration of complex physiological interactions, bioavailability, and individual patient variations that cannot be fully replicated in laboratory settings.

Further research is needed to evaluate the effectiveness and safety of Traditional Chinese Medicine modalities in cancer treatment. Therefore, rigorous clinical trials remain essential to validate these mechanistic insights and establish the true therapeutic potential of Traditional Chinese Medicine compounds in non-Hodgkin lymphoma treatment. Future clinical investigations should prioritize standardized outcome measures that comprehensively assess the impact of TCM interventions on patients' quality of life, progression-free survival, and overall therapeutic response to establish evidence-based integration protocols. Such research can help to establish TCM as a viable and effective treatment option for cancer patients.

Disclaimer (Artificial intelligence)

Author(s) hereby declare that generative AI technologies such as Large Language Models, etc. have been used during the writing or editing of manuscripts. This explanation will include the name, version, model, and source of the generative AI technology and as well as all input prompts provided to the generative AI technology

Details of the AI usage are given below:

1.Large Language Model (Claude 3.5) for grammar and spelling assistance.

**Purpose:** Grammar checking, spelling correction, and language refinement of the manuscript text **Input Prompts:** Sections of manuscript text were provided to the AI with requests to "check grammar and spelling" and "improve language clarity while maintaining scientific accuracy”

References

1. Miranda-Filho, A., et al., *Global patterns and trends in the incidence of non-Hodgkin lymphoma.* Cancer Causes Control, 2019. **30**(5): p. 489-499.
2. Howe, H.L., et al., *Annual report to the nation on the status of cancer (1973 through 1998), featuring cancers with recent increasing trends.* J Natl Cancer Inst, 2001. **93**(11): p. 824-42.
3. Levi, F., et al., *Trends in mortality from non-Hodgkin's lymphomas.* Leuk Res, 2002. **26**(10): p. 903-8.
4. Jemal, A., et al., *Annual report to the nation on the status of cancer, 1975-2001, with a special feature regarding survival.* Cancer, 2004. **101**(1): p. 3-27.
5. Levi, F., et al., *Cancer mortality in Europe, 1995-1999, and an overview of trends since 1960.* Int J Cancer, 2004. **110**(2): p. 155-69.

1. van de Schans, S.A.M., et al., *Diverging trends in incidence and mortality, and improved survival of non-Hodgkin's lymphoma, in the Netherlands, 1989-2007.* Ann Oncol, 2012. **23**(1): p. 171-182.

1. Balducci, L. and M. Extermann, *Cancer and aging. An evolving panorama.* Hematol Oncol Clin North Am, 2000. **14**(1): p. 1-16.

1. Esau, D., *Viral Causes of Lymphoma: The History of Epstein-Barr Virus and Human T-Lymphotropic Virus 1.* Virology (Auckl), 2017. **8**: p. 1178122X17731772.

1. Singh, R., et al., *Non-Hodgkin's lymphoma: A review.* J Family Med Prim Care, 2020. **9**(4): p. 1834-1840.

1. Suarez, F. and M. Lecuit, *Infection-associated non-Hodgkin lymphomas.* Clin Microbiol Infect, 2015. **21**(11): p. 991-7.

1. Shankland, K.R., J.O. Armitage, and B.W. Hancock, *Non-Hodgkin lymphoma.* Lancet, 2012. **380**(9844): p. 848-57.

1. Otter, R., et al., *Primary extranodal and nodal non-Hodgkin's lymphoma. A survey of a population-based registry.* Eur J Cancer Clin Oncol, 1989. **25**(8): p. 1203-10.

1. Groves, F.D., et al., *Cancer surveillance series: non-Hodgkin's lymphoma incidence by histologic subtype in the United States from 1978 through 1995.* J Natl Cancer Inst, 2000. **92**(15): p. 1240-51.

1. Thandra, K.C., et al., *Epidemiology of Non-Hodgkin's Lymphoma.* Med Sci (Basel), 2021. **9**(1).

1. Ekstrom-Smedby, K., *Epidemiology and etiology of non-Hodgkin lymphoma--a review.* Acta Oncol, 2006. **45**(3): p. 258-71.

1. Suzumiya, J., *Current status and progress of lymphoma research in East Asian countries: Introduction and planning.* Int J Hematol, 2018. **107**(4): p. 392-394.

1. Sun, H., et al., *Global, regional and national burden of non-Hodgkin lymphoma from 1990 to 2017: estimates from global burden of disease study in 2017.* Ann Med, 2022. **54**(1): p. 633-645.

1. Bray, F., et al., *Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries.* CA Cancer J Clin, 2018. **68**(6): p. 394-424.

1. Liu, W., et al., *Mortality Rate of Lymphoma in China, 2013-2020.* Front Oncol, 2022. **12**: p. 902643.

1. Bosetti, C., et al., *Incidence and mortality from non-Hodgkin lymphoma in Europe: the end of an epidemic?* Int J Cancer, 2008. **123**(8): p. 1917-23.

1. Cai, W., et al., *Trends Analysis of Non-Hodgkin Lymphoma at the National, Regional, and Global Level, 1990-2019: Results From the Global Burden of Disease Study 2019.* Front Med (Lausanne), 2021. **8**: p. 738693.

1. Detourmignies, L., et al., *Population-based incidence of lymphomas in the French Nord-Pas-de-Calais region between 2001 and 2005: Annual estimations and spatial analysis.* Rev Epidemiol Sante Publique, 2019. **67**(5): p. 319-327.

1. International Non-Hodgkin's Lymphoma Prognostic Factors, P., *A predictive model for aggressive non-Hodgkin's lymphoma.* N Engl J Med, 1993. **329**(14): p. 987-94.

1. Nie, J., et al., *Efficacy of traditional Chinese medicine in treating cancer.* Biomed Rep, 2016. **4**(1): p. 3-14.

1. Wang, Y., et al., *Strategies and techniques for multi-component drug design from medicinal herbs and traditional Chinese medicine.* Curr Top Med Chem, 2012. **12**(12): p. 1356-62.

1. Liu, S.H. and Y.C. Cheng, *Old formula, new Rx: the journey of PHY906 as cancer adjuvant therapy.* J Ethnopharmacol, 2012. **140**(3): p. 614-23.

1. Ardeshna, K.M., et al., *Long-term effect of a watch and wait policy versus immediate systemic treatment for asymptomatic advanced-stage non-Hodgkin lymphoma: a randomised controlled trial.* Lancet, 2003. **362**(9383): p. 516-22.

1. Ansell, S.M. and J. Armitage, *Non-Hodgkin lymphoma: diagnosis and treatment.* Mayo Clin Proc, 2005. **80**(8): p. 1087-97.

1. Yahalom, J., *Radiotherapy of follicular lymphoma: updated role and new rules.* Curr Treat Options Oncol, 2014. **15**(2): p. 262-8.

1. Mellman, I., G. Coukos, and G. Dranoff, *Cancer immunotherapy comes of age.* Nature, 2011. **480**(7378): p. 480-9.

1. Bezombes, C. and P. Perez-Galan, *Immunotherapies in Non-Hodgkin's Lymphoma.* Cancers (Basel), 2021. **13**(14).

1. Qi, F., et al., *The advantages of using traditional Chinese medicine as an adjunctive therapy in the whole course of cancer treatment instead of only terminal stage of cancer.* Biosci Trends, 2015. **9**(1): p. 16-34.

1. Wang, J., et al., *A review of traditional Chinese medicine for treatment of glioblastoma.* Biosci Trends, 2020. **13**(6): p. 476-487.

1. Skubnik, J., et al., *Vincristine in Combination Therapy of Cancer: Emerging Trends in Clinics.* Biology (Basel), 2021. **10**(9).

1. Xiang, Y.Z., et al., *A comparison of the ancient use of ginseng in traditional Chinese medicine with modern pharmacological experiments and clinical trials.* Phytother Res, 2008. **22**(7): p. 851-8.

1. Ru, W., et al., *Chemical constituents and bioactivities of Panax ginseng (C. A. Mey.).* Drug Discov Ther, 2015. **9**(1): p. 23-32.

1. Lee, M.H., et al., *Dammarenediol-II production confers TMV tolerance in transgenic tobacco expressing Panax ginseng dammarenediol-II synthase.* Plant Cell Physiol, 2012. **53**(1): p. 173-82.

1. Leung, K.W. and A.S. Wong, *Pharmacology of ginsenosides: a literature review.* Chin Med, 2010. **5**: p. 20.

1. Lim, W., K.W. Mudge, and F. Vermeylen, *Effects of population, age, and cultivation methods on ginsenoside content of wild American ginseng (Panax quinquefolium).* J Agric Food Chem, 2005. **53**(22): p. 8498-505.

1. Schlag, E.M. and M.S. McIntosh, *Ginsenoside content and variation among and within American ginseng (Panax quinquefolius L.) populations.* Phytochemistry, 2006. **67**(14): p. 1510-9.

1. Wang, C.Z., et al., *Ginseng Metabolites on Cancer Chemoprevention: An Angiogenesis Link?* Diseases, 2015. **3**(3): p. 193-204.

1. Cho, J.Y., et al., *Ginsenosides from Panax ginseng differentially regulate lymphocyte proliferation.* Planta Med, 2002. **68**(6): p. 497-500.

1. Park, J.G., et al., *Korean Red Ginseng water extract arrests growth of xenografted lymphoma cells.* J Ginseng Res, 2016. **40**(4): p. 431-436.

1. Baek, K.S., et al., *Comparison of anticancer activities of Korean Red Ginseng-derived fractions.* J Ginseng Res, 2017. **41**(3): p. 386-391.

1. Kang, S. and H. Min, *Ginseng, the 'Immunity Boost': The Effects of Panax ginseng on Immune System.* J Ginseng Res, 2012. **36**(4): p. 354-68.

1. Jo, S., et al., *Korean red ginseng extract induces proliferation to differentiation transition of human acute promyelocytic leukemia cells via MYC-SKP2-CDKN1B axis.* J Ethnopharmacol, 2013. **150**(2): p. 700-7.

1. Tung, N.H., et al., *Steamed ginseng-leaf components enhance cytotoxic effects on human leukemia HL-60 cells.* Chem Pharm Bull (Tokyo), 2010. **58**(8): p. 1111-5.

1. Chen, S., et al., *Ginseng and anticancer drug combination to improve cancer chemotherapy: a critical review.* Evid Based Complement Alternat Med, 2014. **2014**: p. 168940.

1. Kim, K.H., et al., *Acidic polysaccharide from Panax ginseng, ginsan, induces Th1 cell and macrophage cytokines and generates LAK cells in synergy with rIL-2.* Planta Med, 1998. **64**(2): p. 110-5.

1. Huang, Y., et al., *Antitumor effect of triptolide in T-cell lymphoblastic lymphoma by inhibiting cell viability, invasion, and epithelial-mesenchymal transition via regulating the PI3K/AKT/mTOR pathway.* Onco Targets Ther, 2018. **11**: p. 769-779.

1. Hua, H.Y., et al., *Arsenic trioxide and triptolide synergistically induce apoptosis in the SKM‑1 human myelodysplastic syndrome cell line.* Mol Med Rep, 2016. **14**(5): p. 4180-4186.

1. Zhang, C., et al., *Inhibitory effect of triptolide on lymph node metastasis in patients with non-Hodgkin lymphoma by regulating SDF-1/CXCR4 axis in vitro.* Acta Pharmacol Sin, 2006. **27**(11): p. 1438-46.

1. Soundararajan, R., et al., *Triptolide: An inhibitor of a disintegrin and metalloproteinase 10 (ADAM10) in cancer cells.* Cancer Biol Ther, 2009. **8**(21): p. 2054-62.

1. Long, C., et al., *Triptolide decreases expression of latency-associated nuclear antigen 1 and reduces viral titers in Kaposi's sarcoma-associated and herpesvirus-related primary effusion lymphoma cells.* Int J Oncol, 2016. **48**(4): p. 1519-30.

1. Zhou, H., et al., *Triptolide inhibits proliferation of Epstein-Barr virus-positive B lymphocytes by down-regulating expression of a viral protein LMP1.* Biochem Biophys Res Commun, 2015. **456**(3): p. 815-20.

1. Huang, X., M. Yang, and J. Jin, *Triptolide enhances the sensitivity of multiple myeloma cells to dexamethasone via microRNAs.* Leuk Lymphoma, 2012. **53**(6): p. 1188-95.

1. Chan, E.W., et al., *Triptolide induced cytotoxic effects on human promyelocytic leukemia, T cell lymphoma and human hepatocellular carcinoma cell lines.* Toxicol Lett, 2001. **122**(1): p. 81-7.

1. Kong, J., et al., *Triptolide induces mitochondria-mediated apoptosis of Burkitt's lymphoma cell via deacetylation of GSK-3beta by increased SIRT3 expression.* Toxicol Appl Pharmacol, 2018. **342**: p. 1-13.

1. Long, C., et al., *Triptolide inhibits human telomerase reverse transcriptase by downregulating translation factors SP1 and c-Myc in Epstein-Barr virus-positive B lymphocytes.* Oncol Lett, 2021. **21**(4): p. 280.

1. Long, C., et al., *Triptolide inhibits transcription of hTERT through down-regulation of transcription factor specificity protein 1 in primary effusion lymphoma cells.* Biochem Biophys Res Commun, 2016. **469**(1): p. 87-93.

1. Baas, J., et al., *Dihydroxyquingdainone Induces Apoptosis in Leukaemia and Lymphoma Cells via the Mitochondrial Pathway in a Bcl-2- and Caspase-3-Dependent Manner and Overcomes Resistance to Cytostatic Drugs In Vitro.* Molecules, 2022. **27**(15).

1. Wang, L., et al., *Enhancing effects of indirubin on the arsenic disulfide-induced apoptosis of human diffuse large B-cell lymphoma cells.* Oncol Lett, 2015. **9**(4): p. 1940-1946.

1. Chebel, A., et al., *Indirubin derivatives inhibit malignant lymphoid cell proliferation.* Leuk Lymphoma, 2009. **50**(12): p. 2049-60.

1. Soltan, M.Y., et al., *Key Role of Reactive Oxygen Species (ROS) in Indirubin Derivative-Induced Cell Death in Cutaneous T-Cell Lymphoma Cells.* Int J Mol Sci, 2019. **20**(5).

1. Marko, D., et al., *Inhibition of cyclin-dependent kinase 1 (CDK1) by indirubin derivatives in human tumour cells.* Br J Cancer, 2001. **84**(2): p. 283-9.

1. Hoessel, R., et al., *Indirubin, the active constituent of a Chinese antileukaemia medicine, inhibits cyclin-dependent kinases.* Nat Cell Biol, 1999. **1**(1): p. 60-7.

1. Damiens, E., et al., *Anti-mitotic properties of indirubin-3'-monoxime, a CDK/GSK-3 inhibitor: induction of endoreplication following prophase arrest.* Oncogene, 2001. **20**(29): p. 3786-97.

1. Knockaert, M., et al., *Independent actions on cyclin-dependent kinases and aryl hydrocarbon receptor mediate the antiproliferative effects of indirubins.* Oncogene, 2004. **23**(25): p. 4400-12.

1. Meijer, L., et al., *GSK-3-selective inhibitors derived from Tyrian purple indirubins.* Chem Biol, 2003. **10**(12): p. 1255-66.

1. Kagialis-Girard, S., et al., *Inhibition of normal lymphocyte proliferation by Indirubin-3'-monoxime: a multifactorial process.* Leuk Lymphoma, 2007. **48**(3): p. 605-15.

1. Springs, A.E. and C.D. Rice, *The Effects of Indirubin-3'-Monoxime, A Novel AHR Ligand, on Stress and Toxicity-Related Gene/Protein Expression in Human U937 Cells Undergoing Differentiation and Activation.* J Immunotoxicol, 2006. **3**(1): p. 1-10.

1. Lee, C.C., et al., *Meisoindigo is a promising agent with in vitro and in vivo activity against human acute myeloid leukemia.* Leuk Lymphoma, 2010. **51**(5): p. 897-905.

1. Xiao, Z., et al., *Indirubin and meisoindigo in the treatment of chronic myelogenous leukemia in China.* Leuk Lymphoma, 2002. **43**(9): p. 1763-8.

1. Choudhury, B., et al., *Anticancer Activity of Garcinia morella on T-Cell Murine Lymphoma Via Apoptotic Induction.* Front Pharmacol, 2016. **7**: p. 3.

1. Boueroy, P., et al., *Antitumor effect of forbesione isolated from Garcinia hanburyi on cholangiocarcinoma in vitro and in vivo.* Oncol Lett, 2016. **12**(6): p. 4685-4698.

1. Shi, X., et al., *Gambogic acid induces apoptosis in diffuse large B-cell lymphoma cells via inducing proteasome inhibition.* Sci Rep, 2015. **5**: p. 9694.

1. Ding, L., et al., *Identification of viral SIM-SUMO2-interaction inhibitors for treating primary effusion lymphoma.* PLoS Pathog, 2019. **15**(12): p. e1008174.

1. Chen, J.J., et al., *Inhibition of autophagy augments the anticancer activity of alpha-mangostin in chronic myeloid leukemia cells.* Leuk Lymphoma, 2014. **55**(3): p. 628-38.

1. Boueroy, P., et al., *Synergistic Effect of Forbesione From Garcinia hanburyi in Combination with 5-Fluorouracil on Cholangiocarcinoma.* Asian Pac J Cancer Prev, 2017. **18**(12): p. 3343-3351.

1. Liang, H., J. Guo, and C.G. Li, *Long-Term Complete Remission of a Patient With Double-Hit Diffuse Large B-Cell Lymphoma Treated by Chemoimmunotherapy and Chinese Herbal Medicine.* Integr Cancer Ther, 2023. **22**: p. 15347354221147515.

1. Huang, L., et al., *Rosmarinic acid inhibits proliferation and migration, promotes apoptosis and enhances cisplatin sensitivity of melanoma cells through inhibiting ADAM17/EGFR/AKT/GSK3beta axis.* Bioengineered, 2021. **12**(1): p. 3065-3076.

1. Sirajudeen, F., et al., *Exploring the Potential of Rosemary Derived Compounds (Rosmarinic and Carnosic Acids) as Cancer Therapeutics: Current Knowledge and Future Perspectives.* Biomol Ther (Seoul), 2024. **32**(1): p. 38-55.

1. Azhar, M.K., et al., *Comprehensive Insights into Biological Roles of Rosmarinic Acid: Implications in Diabetes, Cancer and Neurodegenerative Diseases.* Nutrients, 2023. **15**(19).

1. Kowalczyk, A., C.I.G. Tuberoso, and I. Jerkovic, *The Role of Rosmarinic Acid in Cancer Prevention and Therapy: Mechanisms of Antioxidant and Anticancer Activity.* Antioxidants (Basel), 2024. **13**(11).

1. Huang, M., et al., *Anti-tumor properties of Prunella Vulgaris.* Current Pharmacology Reports, 2015. **1**: p. 401-419.

1. Liu, Y., et al., *Rosmarinic acid inhibits cell proliferation, migration, and invasion and induces apoptosis in human glioma cells.* Int J Mol Med, 2021. **47**(5).

1. Mao, X., et al., *A study on inhibitory effect of Spica prunellae extract on T lymphoma cell EL-4 tumour.* Afr J Tradit Complement Altern Med, 2013. **10**(5): p. 318-24.

1. Fang, Y., et al., *Spica Prunellae extract suppresses the growth of human colon carcinoma cells by targeting multiple oncogenes via activating miR-34a.* Oncol Rep, 2017. **38**(3): p. 1895-1901.

1. XH, W., H. SONG, and A. SUI, *To explore the mechanism of Prunella vulgaris on lymphoma based on network pharmacology and molecular docking.* World Cancer Res J, 2021.

1. Mak, W.C.K., *Review of the Studies on the Anti-tumoral Effect of Prunella vulgaris.* Journal of Biosciences and Medicines, 2021.

1. Ma, J.T., et al., *Advances in Research on Chemical Constituents and Their Biological Activities of the Genus Actinidia.* Nat Prod Bioprospect, 2021. **11**(6): p. 573-609.

1. Reyes, F.J., et al., *(2Alpha,3beta)-2,3-dihydroxyolean-12-en-28-oic acid, a new natural triterpene from Olea europea, induces caspase dependent apoptosis selectively in colon adenocarcinoma cells.* FEBS Lett, 2006. **580**(27): p. 6302-10.

1. Woo, H.J., et al., *Apoptogenic activity of 2alpha,3alpha-dihydroxyurs-12-ene-28-oic acid from Prunella vulgaris var. lilacina is mediated via mitochondria-dependent activation of caspase cascade regulated by Bcl-2 in human acute leukemia Jurkat T cells.* J Ethnopharmacol, 2011. **135**(3): p. 626-35.

1. Wang, O., et al., *Anticancer activity of 2alpha, 3alpha, 19beta, 23beta-Tetrahydroxyurs-12-en-28-oic acid (THA), a novel triterpenoid isolated from Sinojackia sarcocarpa.* PLoS One, 2011. **6**(6): p. e21130.

1. Kumagai, T., et al., *Scutellaria baicalensis, a herbal medicine: anti-proliferative and apoptotic activity against acute lymphocytic leukemia, lymphoma and myeloma cell lines.* Leuk Res, 2007. **31**(4): p. 523-30.

1. Kumagai, T., et al., *Scutellaria Baicalensis, a Herbal Medicine: Antitumor Activity Against Acute Lymphocytic Leukemia, Lymphoma and Myeloma in Vitro*. 2004, American Society of Hematology.
2. Tao, Y., et al., *Baicalin, the major component of traditional Chinese medicine Scutellaria baicalensis induces colon cancer cell apoptosis through inhibition of oncomiRNAs.* Sci Rep, 2018. **8**(1): p. 14477.
3. Ye, F., et al., *Anticancer activity of Scutellaria baicalensis and its potential mechanism.* J Altern Complement Med, 2002. **8**(5): p. 567-72.
4. Feng, Y., et al., *Novel function of scutellarin in inhibiting cell proliferation and inducing cell apoptosis of human Burkitt lymphoma Namalwa cells.* Leuk Lymphoma, 2012. **53**(12): p. 2456-64.
5. Vesaghhamedani, S., et al., *From traditional medicine to modern oncology: Scutellarin, a promising natural compound in cancer treatment.* Prog Biophys Mol Biol, 2023. **180-181**: p. 19-27.
6. Cao, P., et al., *Scutellarin suppresses proliferation and promotes apoptosis in A549 lung adenocarcinoma cells via AKT/mTOR/4EBP1 and STAT3 pathways.* Thorac Cancer, 2019. **10**(3): p. 492-500.
7. Morshed, A., et al., *Baicalein as Promising Anticancer Agent: A Comprehensive Analysis on Molecular Mechanisms and Therapeutic Perspectives.* Cancers (Basel), 2023. **15**(7).
8. Verma, E., et al., *Potential of baicalein in the prevention and treatment of cancer: A scientometric analyses based review.* Journal of Functional Foods, 2021. **86**: p. 104660.
9. Rahmani, A.H., et al., *The Multifaceted Role of Baicalein in Cancer Management through Modulation of Cell Signalling Pathways.* Molecules, 2022. **27**(22).
10. Huang, Y., et al., *Down-regulation of the PI3K/Akt signaling pathway and induction of apoptosis in CA46 Burkitt lymphoma cells by baicalin.* J Exp Clin Cancer Res, 2012. **31**(1): p. 48.
11. Sui, X., et al., *Baicalin Induces Apoptosis and Suppresses the Cell Cycle Progression of Lung Cancer Cells Through Downregulating Akt/mTOR Signaling Pathway.* Front Mol Biosci, 2020. **7**: p. 602282.
12. Wang, H., et al., *Baicalin extracted from Huangqin (Radix Scutellariae Baicalensis) induces apoptosis in gastric cancer cells by regulating B cell lymphoma (Bcl-2)/Bcl-2-associated X protein and activating caspase-3 and caspase-9.* J Tradit Chin Med, 2017. **37**(2): p. 229-5.
13. Wang, R., et al., *Baicalin and baicalein in modulating tumor microenvironment for cancer treatment: A comprehensive review with future perspectives.* Pharmacol Res, 2024. **199**: p. 107032.
14. Wu, X., et al., *Wogonin as a targeted therapeutic agent for EBV (+) lymphoma cells involved in LMP1/NF-kappaB/miR-155/PU.1 pathway.* BMC Cancer, 2017. **17**(1): p. 147.
15. Xu, P.P., et al., *Wogonin Inhibits Growth of Mantle Cell Lymphoma Cells through Nuclear Factor-kappaB Signaling Pathway.* Chin Med J (Engl), 2018. **131**(4): p. 495-497.
16. Polier, G., et al., *Wogonin and related natural flavones are inhibitors of CDK9 that induce apoptosis in cancer cells by transcriptional suppression of Mcl-1.* Cell Death Dis, 2011. **2**(7): p. e182.
17. Wu, X., et al., *Advances of wogonin, an extract from Scutellaria baicalensis, for the treatment of multiple tumors.* Onco Targets Ther, 2016. **9**: p. 2935-43.
18. Li, Z.J., et al., *Cytotoxic effect of icaritin and its mechanisms in inducing apoptosis in human burkitt lymphoma cell line.* Biomed Res Int, 2014. **2014**: p. 391512.
19. Mo, Z.T., et al., *Icariin Attenuates OGD/R-Induced Autophagy via Bcl-2-Dependent Cross Talk between Apoptosis and Autophagy in PC12 Cells.* Evid Based Complement Alternat Med, 2016. **2016**: p. 4343084.
20. Wu, T., et al., *Icaritin induces lytic cytotoxicity in extranodal NK/T-cell lymphoma.* J Exp Clin Cancer Res, 2015. **34**(1): p. 17.
21. Liu, X., et al., *Case report: A case study on the treatment using icaritin soft capsules in combination with lenvatinib achieving impressive PR and stage reduction in unresectable locally progressive pancreatic cancer and a literature review.* Front Genet, 2023. **14**: p. 1167470.
22. Xue, Z., et al., *Investigating the effect of Icaritin on hepatocellular carcinoma based on network pharmacology.* Front Pharmacol, 2023. **14**: p. 1208495.
23. Yang, X.J., Y.M. Xi, and Z.J. Li, *Icaritin: A Novel Natural Candidate for Hematological Malignancies Therapy.* Biomed Res Int, 2019. **2019**: p. 4860268.
24. Ho, C.Y., et al., *Differential effect of Coriolus versicolor (Yunzhi) extract on cytokine production by murine lymphocytes in vitro.* Int Immunopharmacol, 2004. **4**(12): p. 1549-57.
25. Habtemariam, S., *Trametes versicolor (Synn. Coriolus versicolor) Polysaccharides in Cancer Therapy: Targets and Efficacy.* Biomedicines, 2020. **8**(5).
26. He, Z., et al., *Polysaccharide-Peptide from Trametes versicolor: The Potential Medicine for Colorectal Cancer Treatment.* Biomedicines, 2022. **10**(11).
27. Ng, T.B., *A review of research on the protein-bound polysaccharide (polysaccharopeptide, PSP) from the mushroom Coriolus versicolor (Basidiomycetes: Polyporaceae).* Gen Pharmacol, 1998. **30**(1): p. 1-4.
28. Dou, H., Y. Chang, and L. Zhang, *Coriolus versicolor polysaccharopeptide as an immunotherapeutic in China.* Prog Mol Biol Transl Sci, 2019. **163**: p. 361-381.
29. Chang, Y., et al., *Preclinical and clinical studies of Coriolus versicolor polysaccharopeptide as an immunotherapeutic in China.* Discov Med, 2017. **23**(127): p. 207-219.
30. Ho, C.Y., et al., Coriolus versicolor (Yunzhi) extract attenuates growth of human leukemia xenografts and induces apoptosis through the mitochondrial pathway. Oncol Rep, 2006. 16(3): p. 609-16.
31. Lau, C.B., et al., Cytotoxic activities of Coriolus versicolor (Yunzhi) extract on human leukemia and lymphoma cells by induction of apoptosis. Life Sci, 2004. 75(7): p. 797-808.
32. Hattori, T.S., et al., Protein-bound polysaccharide K induced apoptosis of the human Burkitt lymphoma cell line, Namalwa. Biomed Pharmacother, 2004. 58(4): p. 226-30.
33. Saleh, M.H., I. Rashedi, and A. Keating, Immunomodulatory Properties of Coriolus versicolor: The Role of Polysaccharopeptide. Front Immunol, 2017. 8: p. 1087.
34. Vannucci, L., et al., Immunostimulatory properties and antitumor activities of glucans (Review). Int J Oncol, 2013. 43(2): p. 357-64.
35. Quayle, K., et al., The TLR2 agonist in polysaccharide-K is a structurally distinct lipid which acts synergistically with the protein-bound beta-glucan. J Nat Med, 2015. 69(2): p. 198-208.
36. Lu, H., et al., Polysaccharide krestin is a novel TLR2 agonist that mediates inhibition of tumor growth via stimulation of CD8 T cells and NK cells. Clin Cancer Res, 2011. 17(1): p. 67-76.
37. Wenner, C.A., et al., Modulation of innate immune cell activation and function by Polysaccharide Krestin (PSK). Planta Medica, 2008. 74(09).
38. Price, L., et al., Stimulation of TNF- α secretion by Polysaccharide Krestin, a Trametes versicolor mushroom extract, is toll-like receptor 4-dependent and dectin-1 independent. Planta Medica, 2008. 74(09).
39. Kang, S.C., et al., Effects of beta-glucans from Coriolus versicolor on macrophage phagocytosis are related to the Akt and CK2/Ikaros. Int J Biol Macromol, 2013. 57: p. 9-16.
40. Taylor, P.R., et al., The beta-glucan receptor, dectin-1, is predominantly expressed on the surface of cells of the monocyte/macrophage and neutrophil lineages. J Immunol, 2002. 169(7): p. 3876-82.

136. Freedman AS, Friedberg JW, Aster JC. Clinical presentation and initial evaluation of non-Hodgkin lymphoma. UpToDate. 2023. Accessed at https://www.uptodate.com/contents/clinical-presentation-and-initial-evaluation-of-non-hodgkin-lymphoma on November 30, 2023.

137. Du, R., Wang, X., Ma, L., Larcher, L. M., Tang, H., Zhou, H., Chen, C., & Wang, T. (2021). Adverse reactions of targeted therapy in cancer patients: A retrospective study of hospital medical data in China. *BMC Cancer*, *21*(1). <https://doi.org/10.1186/s12885-021-07946-x>

138. Ghemrawi, R., Abuamer, L., Kremesh, S., Hussien, G., Ahmed, R., Mousa, W., Khoder, G., & Khair, M. (2024). Revolutionizing cancer treatment: Recent advances in immunotherapy. Biomedicines, 12(9), 2158. <https://doi.org/10.3390/biomedicines12092158>

139. Suresh, T., Lee, L. X., Joshi, J., & Barta, S. K. (2014). New antibody approaches to lymphoma therapy. Journal of Hematology &amp; Oncology, 7(1). <https://doi.org/10.1186/s13045-014-0058-4>

140. Cai, P., Hao, J., Wang, D., & Xu, J. (2017). Comparative efficacy of different chemotherapies for non-Hodgkin Lymphoma: A Network-meta analysis. Oncotarget, 8(53), 91238–91247. <https://doi.org/10.18632/oncotarget.20437>

141. Klener, P., & Klanova, M. (2020). Drug resistance in Non-Hodgkin lymphomas. International Journal of Molecular Sciences, 21(6), 2081. <https://doi.org/10.3390/ijms21062081>

142. Mounier, N., Anthony, S., Busson, R., Thieblemont, C., Nerich, V., Ribrag, V., Castera, M., Tilly, H., Haioun, C., Casasnovas, R.-O., Morschhauser, F., Feugier, P., Delarue, R., Ysebaert, L., Sebban, C., Broussais, F., Damaj, G., Jais, J.-P., Henry-Amar, M., & Salles, G. A. (2016). Long term toxicity and fatigue after treatment for non-Hodgkin Lymphoma (NHL): An analysis of twelve collaborative lymphoma study association (LYSA) trials, the Simonal study. Journal of Clinical Oncology, 34(15\_suppl), 7518–7518. <https://doi.org/10.1200/jco.2016.34.15_suppl.7518>

143. Gunatilaka, A. A. (2006). Natural products from plant-associated microorganisms:  distribution, structural diversity, bioactivity, and implications of their occurrence. Journal of Natural Products, 69(3), 509–526. <https://doi.org/10.1021/np058128n>

144. Cai, C., Wu, Q., Hong, H., He, L., Liu, Z., Gu, Y., Zhang, S., Wang, Q., Fan, X., & Fang, J. (2021). In silico identification of natural products from traditional Chinese Medicine for Cancer Immunotherapy. Scientific Reports, 11(1). <https://doi.org/10.1038/s41598-021-82857-2>

145. Zhong, H., Han, L., Lu, R.-Y., & Wang, Y. (2022). Antifungal and immunomodulatory ingredients from traditional Chinese medicine. Antibiotics, 12(1), 48. <https://doi.org/10.3390/antibiotics12010048>

146. Ahmad, M., Tahir, M., Hong, Z., Zia, M. A., Rafeeq, H., Ahmad, M. S., Rehman, S. ur, & Sun, J. (2025). Plant and marine-derived natural products: Sustainable pathways for future drug discovery and therapeutic development. Frontiers in Pharmacology, 15. <https://doi.org/10.3389/fphar.2024.1497668>

147. Chi, Y., Wang, Y., Ji, M., Li, Y., Zhu, H., Yan, Y., Fu, D., Zou, L., & Ren, B. (2022). Natural products from traditional medicine as promising agents targeting at different stages of oral biofilm development. Frontiers in Microbiology, 13. <https://doi.org/10.3389/fmicb.2022.955459>

148. Palombo, E. A. (2011). Traditional medicinal plant extracts and natural products with activity against oral bacteria: Potential application in the prevention and treatment of oral diseases. Evidence-Based Complementary and Alternative Medicine, 2011(1). <https://doi.org/10.1093/ecam/nep067>

149. Hong, Z., Xiao, M., Yang, Y., Han, Z., Cao, Y., Li, C., Wu, Y., Gong, Q., Zhou, X., Xu, D., Meng, L., Ma, D., & Zhou, J. (2011). Arsenic disulfide synergizes with the phosphoinositide 3-kinase inhibitor PI-103 to eradicate acute myeloid leukemia stem cells by inducing differentiation. Carcinogenesis, 32(10), 1550–1558. <https://doi.org/10.1093/carcin/bgr176>

150. WANG, L., LI, X., LIU, X., LU, K., CHEN, N., LI, P., LV, X., & WANG, X. (2015). Enhancing effects of Indirubin on the arsenic disulfide-induced apoptosis of human diffuse large B-cell lymphoma cells. Oncology Letters, 9(4), 1940–1946. <https://doi.org/10.3892/ol.2015.2941>

151. Chen, C., Wang, L., Liu, Y., Du, S., & Teng, Q. (2024). Arsenic disulfide promoted the demethylation of ptpl1 in diffuse large B cell lymphoma cells. PeerJ, 12. <https://doi.org/10.7717/peerj.17363>

152. HUANG, M., LIN, H.-S., LEE, Y. S., & HO, P. C. (2014). Evaluation of Meisoindigo, an indirubin derivative: In vitro antileukemic activity and in vivo pharmacokinetics. International Journal of Oncology, 45(4), 1724–1734. <https://doi.org/10.3892/ijo.2014.2548>

153. Xiao, Z., Hao, Y., Liu, B., & Qian, L. (2002). Indirubin and Meisoindigo in the treatment of chronic myelogenous leukemia in China. Leukemia &amp; Lymphoma, 43(9), 1763–1768. <https://doi.org/10.1080/1042819021000006295>

154. Nair, R., Arora, N., & Mallath, M. K. (2016). Epidemiology of non-hodgkin’s lymphoma in India. Oncology, 91(Suppl. 1), 18–25. <https://doi.org/10.1159/000447577>

155. Sandhu, D. S., Sharma, A., & Kumar, L. (2018). Non-Hodgkin’s lymphoma in Northern India: An analysis of clinical features of 241 cases. Indian Journal of Medical and Paediatric Oncology, 39(01), 42–45. https://doi.org/10.4103/ijmpo.ijmpo\_36\_17

156. Mishra, P., Prashar, M., Rehman, N., Sinha, A., & Raman, D. K. (2023). Primary extranodal lymphomas: Five-year experience from a tertiary care center of North India. Indian Journal of Cancer, 61(1), 16–21. https://doi.org/10.4103/ijc.ijc\_1267\_20

157. Pai, A., Kannan, T., Balambika, R., & Vasini, V. (2017). A study of clinical profile of primary extranodal lymphomas in a Tertiary Care Institute in South India. Indian Journal of Medical and Paediatric Oncology, 38(3), 251. <https://doi.org/10.4103/ijmpo.ijmpo_82_16>

158. Hanahan, D., & Weinberg, R. A. (2000). The hallmarks of cancer. Cell, 100(1), 57–70. <https://doi.org/10.1016/s0092-8674(00)81683-9>

159. Hsieh, H.-Y., Chiu, P.-H., & Wang, S.-C. (2011). Epigenetics in traditional Chinese pharmacy: A bioinformatic study at Pharmacopoeia scale. Evidence-Based Complementary and Alternative Medicine, 2011(1). https://doi.org/10.1093/ecam/neq050