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The significant role of glycosides in Leukemia: Mechanistic and Clinical prospects

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ABSTRACT: Leukemia is a type of cancer that affects the lymphatic system and bone marrow. It is a heterogeneous disorder with two main types: acute and chronic leukemia. Acute leukemia is more aggressive and severe in children, whereas chronic leukemia mainly affects adults and is comparatively less aggressive. If left untreated, both types can lead to serious illness and even death. Although there are treatment options available such as chemotherapy, radiation therapy, immunotherapy, and the popular CART therapy, leukemia remains a challenging disease worldwide. These existing strategies have limitations, including frequent relapses and toxicity, which highlights the need to explore alternative therapeutic approaches. Glycosides, which are secondary metabolites found in plants, show promise as potential solutions. These substances have a wide range of therapeutic applications, high bioavailability, and low toxicity. They can be used to treat various diseases, both communicable and non-communicable, making them an intriguing class of drugs. However, further research is necessary to uncover their potential value in treating cancer, particularly leukemia. This study aims to investigate the mechanisms of action, effectiveness, and utilization of different glycosides in the treatment of leukemia, while considering the current limitations of existing therapies.

Keywords: Leukemia; Glycoside; Cardiac glycosides; Cancer; Chemotherapy limitations

1. INTRODUCTION

HAEMATOLOGICAL malignancies encompass cancers that impact the lymph nodes, bone marrow, and blood cells, and their interconnectedness through the immune system often results in the spread of sickness across these tissues. Examples of haematological cancers include multiple myeloma, lymphoma, and leukemia (Torkaman et al., 2011). Leukemia comprises a group of disorders characterized by the abnormal accumulation of malignant white blood cells in the bone marrow and bloodstream (Ravandi et al., 2018). The most common types of leukemia include acute myeloid leukemia (AML), acute lymphocytic leukemia (ALL),

chronic myeloid leukemia (CML), and chronic lymphocytic leukemia (CLL) (Bibi et al., 2020).

AML is characterized by an increase in the number of myeloid cells in the bone marrow and a disruption in their maturation process. This condition typically leads to insufficient blood cell production, low levels of granulocytes and platelets, and anemia, sometimes accompanied by high white blood cell counts (Lowenberg et al., 1999). The primary treatments for AML consist of chemotherapy, radiotherapy, and hematopoietic stem cell transplantation (HSCT). Chemotherapy is the mainstay treatment for all AML patients, but its effectiveness is hindered by drug resistance and the occurrence of relapse (Lu et al., 2018). Leukemic stem cells (LSCs) exhibit relatively higher resistance to standard therapies such as chemotherapy and radiation (Farzaneh et al., 2023; Laverdière et al., 2018). LSCs are believed to be the primary cause of AML relapse due to their capacity for self-renewal and ability to remain dormant for extended periods, thereby acquiring greater resistance to conventional cancer treatments (Costa et al., 2023).

ALL is a malignancy of B or T lymphoblasts characterized by uncontrolled proliferation of abnormal and immature lymphocytes and their precursors. This process eventually replaces the normal components of the bone marrow and other lymphoid organs, giving rise to distinct disease manifestations (Puckett and Chan, 2022). ALL is an aggressive form of cancer that primarily affects children (Lai et al., 2000). Exposure to chemotherapy and radiotherapy has been associated with the development of ALL [9]. Hematopoietic stem cell transplantation (HSCT) is currently the only effective curative treatment for AL (Yanir et al., 2018).

CLL involves the accumulation of mature B lymphocytes in the bone marrow and secondary lymphoid organs (Ghia et al., 2007). It is one of the most prevalent forms of leukemia that primarily affects older individuals and exhibits diverse clinical progression patterns (Hallek and Al-Sawaf, 2021). The fundamental role of B-cell receptor (BCR) signaling in the proliferation and survival of CLL cells has significantly enhanced our understanding of the disease's underlying mechanisms. Numerous research studies have demonstrated the critical involvement of both antigen-dependent and antigen-independent BCR signaling in the development of CLL (Jones and Byrd, 2014).

Chronic myeloid leukemia (CML) is characterized by the abnormal growth of white blood cells and is treated using tyrosine kinase inhibitors (TKIs) that target the abnormal protein produced by the BCR-ABL gene responsible for driving cancer cell growth (Houshmand et al., 2019). Imatinib, Nilotinib, Dasatinib, and Bosutinib are commonly employed as first-line TKIs in the treatment of CML (Hsieh et al., 2021). Imatinib, the initial TKI approved for CML, effectively inhibits the BCR-ABL tyrosine kinase, leading to remission and improved long-term survival rates for CML patients (Trinh, 2020). However, some patients may develop resistance to imatinib over time, necessitating the use of alternative therapies (Aranda-Tavío et al., 2021). Nilotinib and dasatinib, classified as second-line TKIs, exhibit greater potency in inhibiting BCR-ABL compared to imatinib and can be used as primary treatments for newly diagnosed CML patients in the chronic phase (Vener et al., 2020).

Glycosides are complex compounds containing carboxylic and dicarboxylic acids, fatty amides, lactones, and sugar molecules. They possess biologically active properties and find applications in various industries, including cosmetics and food, due to their antiseptic and anticancer activities (Feng et al., 2020). Glycosides play a regulatory role in biological systems, influencing cell structure, function, and stability, and also serve as recognition motifs such as blood group antigens (Hayes and Pietruszka, 2017). O-glycoside and C-glycoside are common glycosylation patterns, and flavonoid glycosides have demonstrated anti-inflammatory, anticancer, and antioxidant activities (Yang et al., 2018). Cardiac glycosides (CGs) are naturally occurring substances that primarily inhibit Na+/K+ ATPase activity. They induce apoptosis and inhibit cancer cell proliferation, regulate ion transport across cell membranes, maintain intracellular ion homeostasis, and have positive inotropic effects in heart failure. CGs show promise in combating human viral infections by targeting host cell proteins and increasing susceptibility to antiviral therapies (Reddy et al., 2020). While CGs have long been used to treat cardiac congestion and certain cardiac arrhythmias, recent studies have highlighted their potential as therapeutic options for cancer. Notably, CGs have demonstrated remarkable efficacy in inhibiting cancer cell proliferation even at low concentrations, making them ideal candidates for high-throughput drug libraries aimed at combating cancer. (Calderón-

Montaño et al., 2014). Cardiotonic steroids (CTs), a subgroup of cardiac glycosides (CGs), are naturally produced in mammals and have traditionally been utilized for the treatment of heart failure. CTs encompass compounds like ouabain and digoxin, with digoxin being a hydrophilic cardenolide and other cardenolides exhibiting varying degrees of hydrophobicity. The physiological effects of endogenous ouabain on blood pressure and cardiac activity align with the "Na+-lag" hypothesis (Schoner and Scheiner-Bobis, 2007). Digoxin has also demonstrated anticancer properties against various types of cancer. When administered to leukemia cells, digoxin induces a significant increase in apoptosis and causes cell cycle arrest in the G2/M phase (Zhang et al., 2017). Furthermore, the administration of cardiac glycosides can trigger a robust immune response against cancer cells, leading to their elimination. Upon cell death, cancer cells release intracellular components such as calreticulin, HMGB1, and ATP, which activate the immune system and facilitate the eradication of cancer cells. CGs have also shown beneficial effects on the nervous system, including neuroprotection, which may be attributed to metabolic inhibition as a protective mechanism against hypoxia (Elmaci et al., 2018). Typically, cancer therapies inhibit the metabolism of cancer cells while simultaneously eliciting an immunological response (Liu et al., 2021). The therapeutic index of chemotherapeutic drugs is influenced by systemic toxicity, necessitating considerations of dose intensification to enhance efficacy while ensuring tolerability. Current treatments for leukemia, such as chemotherapy, targeted therapy, radiation therapy, bone marrow transplant, and immunotherapy, have limitations and are associated with various side effects. This article emphasizes the effects of glycosides and highlights their significance in the context of leukemia.

2. THERAPEUTIC LIMITATIONS

The type of leukemia, age and general health of the patient, and stage of cancer are the predominant factors that must be considered in determining the best treatment plan. Chemotherapy (Freireich et al., 1961), immunotherapy (Van Driessche et al., 2005), radiation therapy (Bakst and Yahalom, 2011), drugs targeted therapy (Ross et al., 2004), chimeric antigen receptor T-cell therapy (Qasim, 2019), and hematopoietic stem cell transplant (Dickinson et al., 2017) are the various treatment options for leukemia. Acute leukemia, either myeloid or lymphoid, is a severe and critical form of leukemia, causing mortality and morbidity because of its rapid progresses (Uras et al., 2020). For AML traditional chemotherapeutic agents like cytosine arabinoside (Ara-C) and anthracyclines seem to have reached the end of their useful lives (Parisi et al., 2002), AML with FLT3 mutations has responded well to therapy that targets FLT3 receptor-associate kinases. However, for the majority of patients, responses are insufficient and short-lived (Kayser and Levis, 2014), concerns regarding CAR-T cell therapy application in AML include strategies for target antigen selection, multiantigen aiming, and considerations regarding cancerous cells environment and immune-suppressive nature of AML gives the technical and financial difficulties (Maucher et al., 2021).

Moreover, there are drawbacks to more aggressive chemotherapy, traditional anti-leukemic drugs, and enhanced supportive care for ALL, including broad-spectrum antibiotics to fight opportunistic infections. A sizable portion of leukaemia-related deaths is brought on by treatment rather than the disease itself, and that is just the beginning of the toxicity strain. Nearly all the treatment options for ALL have been limited due to premium technological innovations, oncogenesis, and drug-resistant mechanisms (Schmiegelow et al., 2017). Adult patients with ALL continue to experience significant complications from CNS prophylaxis recurrence during drug-induced treatment. These hold some reasons, i.e., mitigation by significant toxicity, such as neurologic aftereffects, a high index of proliferating cells, and chromosomal abnormalities (Jabbour et al., 2010). Substantial difficulty emerged in increasing chemotherapy dosages for adult ALL patients in a developing nation of financial difficulties, and some difficulties emerged from a lack of resources to manage toxicities and prolonged cytopenia associated with treatment, which resulted in infections that significantly increased morbidity and mortality (Jain et al., 2018). Most attempts to treat ALL with donor lymphocyte infusion following allogeneic stem cell transplantation have been unsuccessful (Nijmeijer et al., 2005). Chronic leukemia, either myeloid or lymphoid, has a long course of disease; however, progression and mortality depend majorly on the secondary complications which arise from untreated or unsuccessful treatment. Therefore, robust treatment

approaches are required (Kurtin, 2021). Tyrosine kinase inhibitors significantly improved the course of CML; however, prolonged treatment requirements in chronicity produced detrimental effects on health, and adverse effects on libido, gestation, motor function, and locomotion, due to long-term medication, which ultimately led to the limitation of its use (Flynn and Atallah, 2016). Conventional CML therapy relied on busulfan or hydroxyurea, neither of which had a significant impact on the disease's course (Talpaz et al., 1983). Immunotherapy in CML produced sophisticated clinical outcomes; notwithstanding widespread optimism, serious drawbacks include significant expense, substantial toxicity in a sizeable portion of patients, and response rates as limited as approx. 40% in clinical trials has emerged this limitation (Music et al., 2018). High-dose chemotherapy with stem cell transplant also has limitations due unavailability of compatible donors (Mojtahedi et al., 2021), and even if the compatible donor requirement is met, pitfall becomes a problem, i.e., marrow graft rejection (Hutt, 2018).

In contrast to lymph node disease, myeloid disease has been more extensively eliminated (O'Brien et al., 2003). Patients with relapsed or resistant CLL experienced a high frequency of long-lasting remissions when taking ibrutinib, the first BTK inhibitor (Byrd et al., 2013). Drug-targeted therapy that includes phosphoinositide 3-kinase (PI3K) inhibitors, Bruton's tyrosine kinase (BTK) inhibitors, and CD20 monoclonal antibodies produced significant drawbacks to their use, which are typically autoimmune in nature, i.e., hepatitis, enteritis/colitis, and pneumonitis (Iskierka-Jażdżewska et al., 2022).

3. THERAPEUTIC POTENTIAL OF GLYCOSIDES

Glycosides are plant-derived secondary metabolites and have several well-known uses. Their structure consists of a sugar called glycone attached to the non-sugar part aglycone or genin through a glycosidic bond. Glycosides are classified by the type of glycosidic linkage, sugar, and non-sugar group (Soto-Blanco, 2022). Glycosides have diverse therapeutic applications, which further classify them as anthraquinone, cardiac, alcoholic, and flavonoid glycosides (Onaolapo and Onaolapo, 2019). Glycosides in medicine as primarily used as an analgesic due to their potential to inhibit diversely present pain mediators with high bioavailability and fewer side effects (Khan et al., 2020). They are also used as an anti-inflammatory agent because they inhibit pro-inflammatory cytokines (Guo et al., 2021), curing acute or chronic (Fürst et al., 2017). The anti-oxidant potential of glycosides was studied and reported to have marked effects (Hopia and Heinonen, 1999) by inhibiting the lipid peroxidation mechanism (Sato et al., 1992). Glycosides have been used as a robust agent in MRSA-resistant strains of Staphylococcus Aureus and VRE-resistant strains of Enterococcus for their antibacterial activities with minimal toxicity (Ml Hossion and Sasaki, 2013). Widely reported ethanolic extracts of Phyllanthus emblica with sesquiterpenoid glycosides showed antiviral activity against the Hepatitis B virus (Linn et al., 2021). Glycosides from different plants extracts were efficiently proven to show neuroprotective activity (Jeong et al., 2012; Zhao et al., 2013) via inhibition of anticholinesterase and decreasing oxidant levels in the body, which helps to provide good cognitive function (Khazdair et al., 2019), acaricidal effect in combination with other compounds have also been reported (Al-Rajhy et al., 2003), they have been used as emetics, diuretics, arrow poisons, contraceptives, and cardiac stimulants for more than 2000 years, Moreover making use of specific cardiac glycosides may be a worthwhile strategy for reducing the rate of cancerous cell proliferation despite their limited therapeutic index (Newman et al., 2008), and its use along with chemotherapeutic agents have been reported to eradicate senescent cells that build up after radiation therapy. However, further research into their application to age-related diseases is necessary (Guerrero et al., 2019). Since diabetes is the world's leading cause of death, using glycosides in its therapy is a promising strategy to manage the disease's complications through different mechanisms, i.e., increasing carbohydrates metabolism, insulin function, glucose utilization, antioxidants bioavailability and decreasing circulating as well as stored lipids, providing the ultimate solution to diabetes and its unwanted effects (Khattak and Khan, 2018). Steviol glycosides are commonly used as flavourings in food and have a variety of therapeutic uses, including effects that lower blood pressure, prevent cancer, and improve oral health (Kurek and Krejpcio, 2019).

Moreover, cardiac glycosides with neuroprotective activity prevent ischemic stroke and focal ischemia by inhibiting Na +, K + -ATPase pump (Wang et al., 2006) and prevent

cerebral injury by inhibiting neuronal apoptosis (She et al., 2019). Various medicinal uses of cardiac glycosides have been reported, i.e., inhibiting cell translation, which lessens influenza virus replication (Amarelle et al., 2019), anti-arrhythmic effects and use in congestive heart failure is well known therapeutic application of cardiac glycosides. Anti-metastatic activity has been reported in vitro, and the fact that cancer cells are more susceptible to these substances suggests that they may be used in treating cancer, as they are involved in multiple transduction mechanisms. Therefore, they stand for a hopeful kind of cancer treatment (Winnicka et al., 2006). Since cardiac glycosides have been reported in numerous studies to have anti-cancer effects, therefore these metabolites may be used as lead compounds to treat a variety of cancers which primarily includes prostate cancer, leukemia, melanoma, hepatocellular carcinoma, fibrosis, lung cancer, breast cancer, and adenocarcinoma (Ayogu and Odoh, 2020). The main goal of glycosides is to stop excessive cell proliferation by specifically targeting over-expressive MYC cells in leukemia, inhibit TNF, scavenge free radicals, and apoptosis induction is a sideways mechanism, as illustrated in **Figure 1**, that overcomes chemoresistance and complications arising from infiltration of organs and bone marrow hypercellularity, (Da Costa et al., 2019).

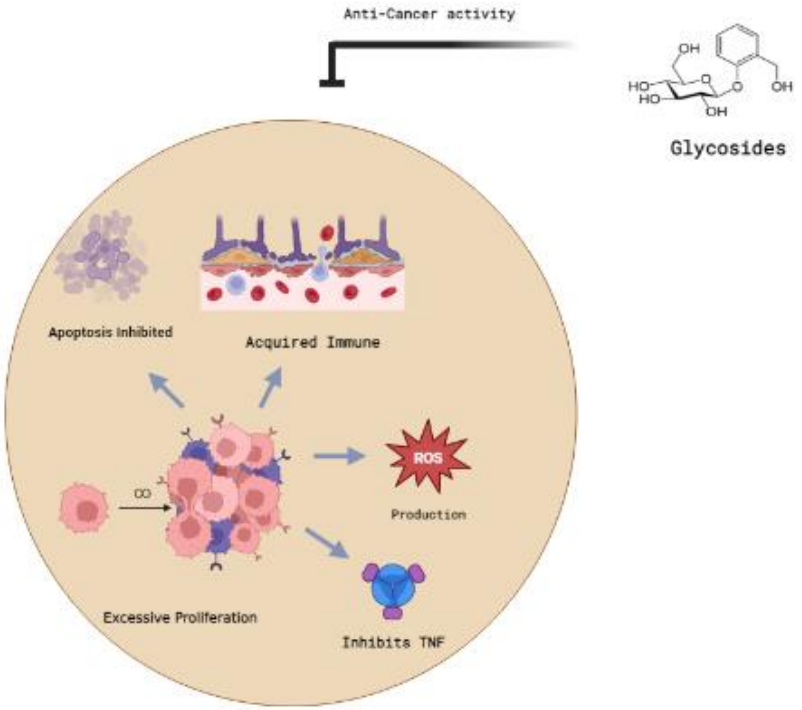

Figure 1: Glycosides anti-cancer potential by halting multiple mechanisms

Triterpene glycosides extracted from sea cucumbers are capable of inducing apoptosis and have unknown mechanisms of anti-cancer activity, but in conjunction with sphingolipids which have known tumour suppressive and anti-proliferative activities, have been reported as an efficient treatment of myeloid leukemia (Yun et al., 2016). The use of glycosides for their anticancer properties in leukemia is entirely viable, but immunomodulation and other activities compile and manage many complications of the disease. Any illness results in the immune system being compromised in some way (Akbay et al., 2003); moreover, the use of these therapeutically active compounds in treating leukemia is further discussed in this study below.

4. GLYCOSIDES IN LEUKAEMIA

Cardiac glycosides, which have long been used to treat heart failure, are now considered potential cancer-fighting agents (Prassas and Diamandis, 2008). Natural products with an unsaturated lactone ring and a steroid-

like structure are cardiac glycosides which are also known as cardiotonic steroids (Sreenivasan et al., 2006). Cardenolides and bufadienolides are the names given to cardiac glycosides that contain lactone 2-furanone and lactone 2-pyrone, respectively. In vitro and ex vivo experiments have shown that some cardiac glycosides, like digitoxin, induce potent and selective anticancer effects (Haux, 1999). Several reports over the years have suggested that cardiac glycosides may have anticancer activity. Cardiac glycosides target Na+/K+-ATPase in cancer by maintaining a sodium-potassium gradient across the plasma membrane, thereby targeting this enzyme. The Na+/K+-ATPase pump is inhibited when Cardiac glycosides bind to it, causing an increase in Ca2+ concentration and intracellular Na+ retention. Endoplasmic reticulum stress is then brought on by decreased Na+/K+-ATPase expression (Kumavath et al., 2021). Geng et al.'s most recent research demonstrated that the Na+/K+ ATPase-dependent cell death induced by cardiac glycoside stops cancer cells from growing, as shown in the **figure 2** and **2a** (Geng et al., 2020).

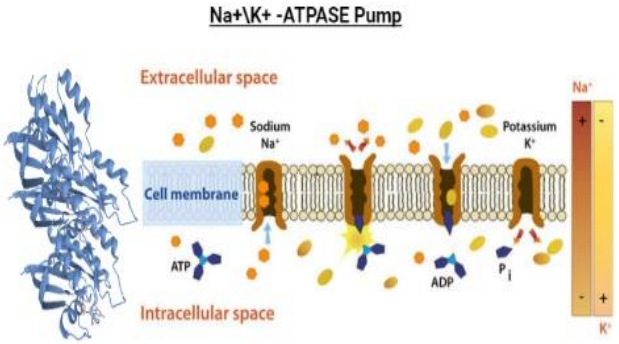

Figure 2: Na+/K+ ATPase pump

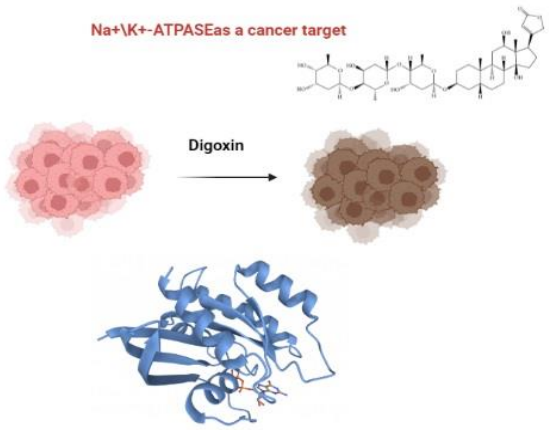

Figure 2a: Na+/K+ ATPase as a cancer target

Even as distinct entities, the various digitalis building blocks possess intriguing properties regarding cell proliferation and metabolism. Irinotecan, one of the most promising chemotherapy drugs, has a lactone moiety that appears to be essential for its anticancer effects (Abang, 1998; Sadzuka et al., 1999). The fact that MDA-MB-231, a receptor-negative breast cancer cell line, was found to be more inhibited than T47D, a receptor-positive cell line, in an in vitro study might suggest that mechanisms other than receptor interaction are at play. Interleukin-2 (IL-2)-stimulated human natural killer cells were used as controls to rule out the possibility that the digitalis effect is only present on cells that are actively proliferating. These cells become highly proliferating lymphokine-activated killer (LAK) cells after being stimulated with IL-2 for three days. However, these cells with the same concentrations of digitalis exhibited neither inhibition nor an increase in apoptosis (Haux et al., 1999). Tamoxifen has been shown to inhibit protein kinase C in the case of glioblastoma. Tamoxifen's PKC inhibition of glioblastoma cells stops them in the G2M phase of the cell cycle and increases their sensitivity to radiation (Baltuch et al., 1993; Zhang et al., 1992).

Zinc pyrithione and Ouabain, which were previously used to treat dermatologic illnesses and heart failure, respectively, were discovered as novel anti-leukemic drugs in a recent study by TAILLER et al. using high throughput screening of 1040 FDA-authorized medicines for anti-leukemic activity (Tailler et al., 2012). AML HL-60 cells were exposed to the pan-tyrosine kinase inhibitor staurosporine, a fundamental inducer of caspase-dependent apoptosis, in order to set up a screening platform for the identification of OUA and PZ as potential anti-leukemic agents (Weil et al., 1996). Co-staining with Hoechst 33342 and a vital dye, which only incorporates into dead cells due to permeabilized plasma membranes, was followed by cell cultures in V-shaped 96-well plates (Galluzzi et al., 2009). Robotized epifluorescence microscopy and automatic image analysis were performed on the cells after they were moved to flat-bottomed 96-well imaging plates coated with poly-L-lysine and placed there for immobilization. Based on this system library of 1040 FDA-approved drugs were screened by Tailler et al., with a final

concentration of 1 [micro]m to find drugs that caused HL-60 cells to apoptosis but did not cause necrosis. Validation testing demonstrated that PZ and OUA are highly effective at inducing several apoptotic hallmarks in a dose- and time-dependent manner: nuclear DNA content reduction, nuclear fragmentation, all of which are signs that nucleases have been activated and indicates loss of clonogenic potential. OUA and PZ's pro-apoptotic effects in HL-60 cells and in three additional AML cell lines (MV4-11, MOLM-13, and KG-1) demonstrate their broad anti-leukemic potential(Tailler et al., 2012).

Laverdiere et al. used existing datasets of drug-gene interactions, and an in-silico analysis of highly prognostic human AML leukemic stem cell gene expression signatures was used to identify compounds expected to target Leukemic stem cell gene programs. A list of 151 anti-Leukemic stem cell candidates was produced after compounds that would inhibit a hematopoietic stem cell gene signature were filtered out, out of which 84 potential compounds at various doses with a novel in vitro Leukemic stem cell assay and discovered 14 drugs that effectively kill human acute myeloid leukaemia LSCs (Laverdière et al., 2018). Namely (terfenadine and astemizole) Antihistamines, (mometasone, halcinonide and budesonide) glucocorticoids, (ouabin, strophanthidin and digoxin) cardiac glycosides), all of which presented multiple hits were tested for their efficacy against human primary AML samples (Laverdière et al., 2018). 8227 AML cells were used to demonstrate that a subset of these candidate molecules could differentially reduce cell populations in the leukemic hierarchy. New compounds that target the therapy-resistant LSC at the root of AML relapse can be found by combining computational analysis of stem cell gene expression signatures with in vitro screening according to the above analysis of Laverdiere and his co-workers (Laverdière et al., 2018).

Xu et al. examine the molecular mechanisms underlying total paeony glycoside (TPG) mediated tumour regression and discovered that TPG had a significant cytotoxic effect on five human cancer cell lines, including Bel-7402 (hepatoma), HCT-8 (colon carcinoma), K562 (erythroleukemia), A549 (lung carcinoma) and Hela (cervical carcinoma). One of the traditional Chinese herbal remedies is Radix Paeoniae Rubra. TPG, which was extracted and purified from the root of Radix Paeoniae Rubra can increase blood flow by inhibiting thrombosis and platelet aggregation and acting as an endothelium-dependent vasodilator on the aorta (Lee et al., 2002). The MTT assay was used to evaluate the K562 cells' viability. In vitro tumour cell lines are inhibited by TPG (Xu et al., 2012). The morphologic changes in four epithelial cancer cell lines (Bel-7402, A549, HCT-8 and Hela) were seen with an upset magnifying lens and showed well-ordered monolayer well. after that, with logarithmic growth times, all five tumour cell lines were chosen for the experiment and incubated for 24 hours with TPG at various concentrations (50, 100, 200, 300, and 400 mg/ml). The MTT assay was used to determine the inhibitory rates of all five tumour cell lines in triplicate. The findings demonstrated that TPG significantly inhibits growth in these five tumour cell lines. These demonstrated that K562 was the most delicate cell line to TPG among all tried cancer cell lines. The feasibility of K562 cells was additionally tried at various time points of (24, 48, and 72 hrs.) with various concentrations of TGF (0, 25, 50, 75, 100, 150, 200, and 400 mg/kg)(Xu et al., 2012). The transplanted tumour tissues were divided into single cells for flow cytometry analysis, and TPG caused K562 cells apoptosis in vivo. The treatment with TPG resulted in a reduction in the tumour volume and weight of the xenografted tumour in nude mice and an inhibition of the proliferation of K562 cell growth in vivo. Initially, we examined cellular morphology, such as nuclear condensation and genomic fragmentation, to determine whether TPG induced apoptosis. The fact that the nude mice in the CTX group weighed the least of the other groups may have been caused by their poor psychosis and lack of appetite. It may be demonstrated that TPG can reduce CTX's toxicity, but according to the author, additional research is required to support the above claims. According to Xu et al., many Chinese medicines may lessen the toxicity of chemotherapy drugs, thereby enhancing healing and extending cancer patients' lives. TPG may be an innovative and promising compound for cancer treatment (Xu et al., 2012).

A few examination bunches have assessed the malignant growth restorative capability of cardiac glycosides by utilizing human non-malignant cells and human cancer cells (Calderón-Montaño et al., 2014). Calderon-Montano et al. observed that ouabain, digitoxin and digoxin cytotoxicity was comparable in melanoma cells (UACC-62) and breast cancer

cells (MCF-7) to that of non-malignant skin cells (VH-10) and non-malignant breast cells (MCF-10) (Calderon-Montano et al., 2014). Kaplan and Clifford discovered that compared to human non-malignant breast cells, human breast cancer cells were even more resistant to toxicity of digitoxin, bufalin and ouabain. However, data also suggest that ouabain, digoxin and digitoxin were roughly ten more cytotoxic to human lung cancer cells (A549) when compared to MRC-5 lung cells (non-malignant) (Calderón-Montaño et al., 2014). Ex-vivo Studies were conducted using cells of adult patients suffering from T-acute or B-precursor ALL, AML, and CLL, along with health donors' peripheral blood mononuclear cells, have revealed that digitoxin (other than ouabain) induces selective cytotoxicity (roughly sevenfold) in cells from patients with T- and B-precursor acute lymphoblastic leukaemia (Hallböök et al., 2011).

Hallbook et al. conducted a study by using cryopreserved cells taken from adult patients with acute myeloid leukaemia (AML), chronic lymphocytic leukaemia (CLL) and acute lymphoblastic leukaemia (ALL). These cells were taken from peripheral blood or bone marrow. Controls were peripheral blood mononuclear cells (PBMCs) from healthy donors. Professor W.T. Beck of St. Jude's Children's Research Hospital, USA, generously donated the T-lymphoblast-like cell line CEM/VBL100 (CCRF-CEM)(Beck et al., 1979), and Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH, Germany, provided the B-precursor Philadelphia-positive cell line SUP-B15 (Naumovski et al., 1988). The cells were divided twice weekly and grown in complete medium (CCRF-CEM in RPMI 1640 and SUP-B15 in McCoy's 5A). Regarding their effects on protein synthesis, the colorectal adenocarcinoma cell lines Hct116, HT29, and CC20 served as comparisons. A fluorometric microculture cytotoxicity assay was used to determine the cytotoxic activity of cardiac glycosides (Larsson et al., 1992). The cytotoxic effect of CGs was studied in CLL, T-ALL, AML, and B-precursor ALL. The same tests were used for leukaemia cell lines SUP-B15 and CCRF-CEM subjected to activity tests for digitoxin, ouabain and digoxin that were comparable to one another. Different glycosides with distinct profiles regarding cardiotoxicity and cellular effects have been developed, and numerous clinical trials have been conducted. SUP-B15 cell line was really sensitive to all cardiac glycosides tested (Hallböök et al., 2011). For instance, a semisynthetic cardenolide known as UNBS-1450 has begun a phase I clinical trial in Belgium and demonstrated promising preclinical activity against NSCLC. AnvirzelTM, an aqueous extract from Nerium oleander, was tested in a phase I trial on patients with refractory solid tumours (Mekhail et al., 2006). In patients with advanced malignant melanoma, studies of the addition of digoxin to combination chemotherapy and immunotherapy have also been initiated; however, the results of these studies have not yet been published(Khan et al., 2007). Utilizing a limited sampling strategy, a comparative pharmacokinetic study of doxorubicin and 4'-epi-doxorubicin in children with acute lymphocytic leukemia was conducted by Eksborg et al. (Eksborg et al., 2000). The pharmacokinetics of Doxorubicin (Dox) and epi-doxorubicin (Epi) in children with acute lymphocytic leukaemia was the subject of this study. 31 patients, including 13 females and 18 males; average age of 5.4 years; a range of 0.73-15.3 years) were examined through a streamlined sampling strategy. The simultaneous administration of the two drugs revealed their distinct pharmacokinetic differences (Eksborg et al., 2000). A brief overview of a few glycosides in leukaemia is shown in **Table 1.**

Table 1: A brief overview of a few glycosides in leukaemia

Glycosides	Mechanism of action	Applications	References
Anthraquinones	Activation of MAPK and PI3K-AKT parallel signalling pathways, Blockade of downstream pathways and regulation of cell cycle and apoptosis.	Signalling module in the PD brain trigger oxidative stress, neuro-inflammation, and apoptosis Used in the treatment of diseases, i.e., cancer, viral	(KUMAR et al., 2015; Sun et al., 2016; Yusuf et al., 2019)

		infections, diabetes, ulcer, and obesity.	
Cardiac glycosides	Inhibition of Na+-K+ pump, Stimulation of DNA topoisomerase I, II and ILD, inhibition of multiple target genes. Blockade of ATP due to higher concentration of K+ Regulation of VEGF expression, Inhibition of MDA-MB-231	Used in the treatment of hypertension and heart failure. Anti-cancer effect on leukaemia Used in the treatment of breast cancer cells	(Fozzard and Sheets, 1985; Prassas and Diamandis, 2008; Reddy et al., 2020; Shibata et al., 2002)
Flavonoids glycosides	Inhibitory effect on α-glycosidase and α-amylase Regulation of MMP-1, -2, and- 9	Used in the treatment of various bacterial infections such as cholera and shigella, Reduction in breast cancer cell lines	(Matsuda et al., 2003; Phromnoi et al., 2009; Tagousop et al., 2018)
Steroidal glycosides	enzymatic hydrolysis with β-glycosidase, Exert inhibition of proliferation, induced apoptosis and autophagy, Regulation of tumours by activating multiple signalling pathways	Exhibit biological activities, i.e., cholesterol-lowering effect, diabetes. Anti-cancer effect in leukemia.	(Arthan et al., 2002; Ikeda et al., 2003; Liu and Kong, 2018; Ya-Zheng et al., 2018)

5. CONCLUSION

Glycosides are natural compounds found in various plants that have been widely used in traditional medicine. Recent research has suggested that glycosides could have a significant role in the development and treatment of leukemia. Mechanistically, glycosides have been shown to induce apoptosis, which is the programmed cell death of cancer cells. This is achieved by interfering with the signaling pathways of cancer cells and disrupting their growth. Additionally, glycosides have been shown to have anti-inflammatory and antioxidant effects, which may be beneficial in reducing the risk of cancer and enhancing overall immune function. From a clinical perspective, glycosides have shown promise as a potential treatment for leukemia. Some studies suggest that they may have a cytotoxic effect on leukemia cells, making them a potential candidate for chemotherapy treatment. Additionally, glycosides have been shown to improve the efficacy of other cancer treatments when used in combination, such as radiation or chemotherapy. This could increase the effectiveness of these treatments while potentially reducing the side effects commonly associated with cancer treatment. Overall, the article suggests that glycosides could have significant implications for understanding and treating leukemia. By exploring the underlying mechanisms by which glycosides influence leukemia, researchers could

gain a deeper understanding of the disease and develop more effective treatments. Additionally, the potential clinical applications of glycosides in leukemia treatment are promising and may provide new avenues for treating this deadly cancer. This research could ultimately have a significant impact on the lives of those affected by leukemia.

REFERENCES

Abang, A.M., 1998. The clinical pharmacology of topoisomerase I inhibitors, Seminars in hematology. pp. 13-21.

Akbay, P., Basaran, A.A., Undeger, U., Basaran, N., 2003. In vitro immunomodulatory activity of flavonoid glycosides from Urtica dioica L. Phytotherapy Research: An International Journal Devoted to Pharmacological and Toxicological Evaluation of Natural Product Derivatives 17(1), 34-37.

Al-Rajhy, D.H., Alahmed, A.M., Hussein, H.I., Kheir, S.M., 2003. Acaricidal effects of cardiac glycosides, azadirachtin and neem oil against the camel tick, Hyalomma dromedarii (Acari: Ixodidae). Pest Management Science 59(11), 1250-1254.

Amarelle, L., Katzen, J., Shigemura, M., Welch, L.C., Cajigas, H., Peteranderl, C., Celli, D., Herold, S., Lecuona, E., Sznajder, J.I., 2019. Cardiac glycosides decrease influenza virus replication by inhibiting cell protein translational machinery. American Journal of Physiology-Lung Cellular and Molecular Physiology 316(6), L1094-L1106.

Aranda-Tavío, H., Recio, C., Martín-Acosta, P., Guerra-Rodríguez, M., Brito-Casillas, Y., Blanco, R., Junco, V., León, J., Montero, J.C., Gandullo-Sánchez, L., 2021. JKST6, a novel multikinase modulator of the BCR-ABL1/STAT5 signaling pathway that potentiates direct BCR-ABL1 inhibition and overcomes imatinib resistance in chronic myelogenous leukemia. Biomedicine & Pharmacotherapy 144, 112330.

Arthan, D., Svasti, J., Kittakoop, P., Pittayakhachonwut, D., Tanticharoen, M., Thebtaranonth, Y., 2002. Antiviral isoflavonoid sulfate and steroidal glycosides from the fruits of Solanum torvum. Phytochemistry 59(4), 459-463.

Ayogu, J.I., Odoh, A.S., 2020. Prospects and Therapeutic Applications of Cardiac Glycosides in Cancer Remediation. ACS Combinatorial Science 22(11), 543-553.

Bakst, R., Yahalom, J., 2011. Radiation therapy for leukemia cutis. Practical radiation oncology 1(3), 182-187.

Baltuch, G.H., Couldwell, W.T., Villemure, J.-G., Yong, V.W., 1993. Protein kinase C inhibitors suppress cell growth in established and low-passage glioma cell lines. A comparison between staurosporine and tamoxifen. Neurosurgery 33(3), 495-501.

Beck, W.T., Mueller, T.J., Tanzer, L.R., 1979. Altered surface membrane glycoproteins in Vinca alkaloid-resistant human leukemic lymphoblasts. Cancer research 39(6_Part_1), 2070-2076.

Bibi, N., Sikandar, M., Ud Din, I., Almogren, A., Ali, S., 2020. IoMT-based automated detection and classification of leukemia using deep learning. Journal of healthcare engineering 2020.

Byrd, J.C., Furman, R.R., Coutre, S.E., Flinn, I.W., Burger, J.A., Blum, K.A., Grant, B., Sharman, J.P., Coleman, M., Wierda, W.G., 2013. Targeting BTK with ibrutinib in relapsed chronic lymphocytic leukemia. New England Journal of Medicine 369(1), 32-42.

Calderon-Montano, J., Burgos-Moron, E., Lopez-Lazaro, M., 2014. The in vivo antitumor activity of cardiac glycosides in mice xenografted with human cancer cells is probably an experimental artifact. Oncogene 33(22), 2947-2948.

Calderón-Montaño, J.M., Burgos-Morón, E., Orta, M.L., Maldonado-Navas, D., García-Domínguez, I., López-Lázaro, M., 2014. Evaluating the cancer therapeutic potential of cardiac glycosides. BioMed research international 2014.

Costa, R.G., Silva, S.L., Dias, I.R., Oliveira, M.d.S., Rodrigues, A.C.B.d.C., Dias, R.B., Bezerra, D.P., 2023. Emerging drugs targeting cellular redox homeostasis to eliminate acute myeloid leukemia stem cells. Redox Biology, 102692.

Da Costa, E.M., Armaos, G., McInnes, G., Beaudry, A., Moquin-Beaudry, G., Bertrand-Lehouillier, V., Caron, M., Richer, C., St-Onge, P., Johnson, J.R., 2019. Heart failure drug proscillaridin A targets MYC overexpressing leukemia through global loss of lysine acetylation. Journal of Experimental & Clinical Cancer Research 38(1), 1-14.

Dickinson, A.M., Norden, J., Li, S., Hromadnikova, I., Schmid, C., Schmetzer, H., Jochem-Kolb, H., 2017. Graft-versus-leukemia effect following hematopoietic stem cell transplantation for leukemia. Frontiers in immunology 8, 496.

Eksborg, S., Palm, C., Björk, O., 2000. A comparative pharmacokinetic study of doxorubicin and 4'-epi-doxorubicin in children with acute lymphocytic leukemia using a limited sampling procedure. Anti-cancer drugs 11(2), 129-136.

Elmaci, İ., Alturfan, E.E., Cengiz, S., Ozpinar, A., Altinoz, M.A., 2018. Neuroprotective and tumoricidal activities of cardiac glycosides. Could oleandrin be a new weapon against stroke and glioblastoma? International Journal of Neuroscience 128(9), 865-877.

Farzaneh, M., Najafi, S., Sheykhi-Sabzehpoush, M., Nezhad Dehbashi, F., Anbiyaee, O., Nasrolahi, A., Azizidoost, S., 2023. The stem cell-specific long non-coding RNAs in leukemia. Clinical and Translational Oncology 25(2), 345-351.

Feng, Y., Yao, M., Wang, Y., Ding, M., Zha, J., Xiao, W., Yuan, Y., 2020. Advances in engineering UDP-sugar supply for recombinant biosynthesis of glycosides in microbes. Biotechnology advances 41, 107538.

Flynn, K.E., Atallah, E., 2016. Quality of Life and Long-Term Therapy in Patients with Chronic Myeloid Leukemia. Current Hematologic Malignancy Reports 11(2), 80-85.

Fozzard, H.A., Sheets, M.F., 1985. Cellular mechanism of action of cardiac glycosides. Journal of the American College of Cardiology 5(5), 10A-15A.

Freireich, E.J., Gehan, E.A., Sulman, D., Boggs, D.R., Frei Iii, E., 1961. The effect of chemotherapy on acute leukemia in the human. Journal of chronic diseases 14(6), 593-608.

Fürst, R., Zündorf, I., Dingermann, T., 2017. New knowledge about old drugs: the anti-inflammatory properties of cardiac glycosides. Planta medica 83(12/13), 977-984.

Galluzzi, L., Aaronson, S.A., Abrams, J., Alnemri, E.S., Andrews, D.W., Baehrecke, E.H., Bazan, N., Blagosklonny, M.V., Blomgren, K., Borner, C., 2009. Guidelines for the use and interpretation of assays for monitoring cell death in higher eukaryotes. Cell Death & Differentiation 16(8), 1093-1107.

Geng, X., Wang, F., Tian, D., Huang, L., Streator, E., Zhu, J., Kurihara, H., He, R., Yao, X., Zhang, Y., 2020. Cardiac glycosides inhibit cancer through Na/K-ATPase-dependent cell death induction. Biochemical Pharmacology 182, 114226.

Ghia, P., Ferreri, A.J., Caligaris-Cappio, F., 2007. Chronic lymphocytic leukemia. Critical reviews in oncology/hematology 64(3), 234-246.

Guerrero, A., Herranz, N., Sun, B., Wagner, V., Gallage, S., Guiho, R., Wolter, K., Pombo, J., Irvine, E.E., Innes, A.J., Birch, J., Glegola, J., Manshaei, S., Heide, D., Dharmalingam, G., Harbig, J., Olona, A., Behmoaras, J., Dauch, D., Uren, A.G., Zender, L., Vernia, S., Martínez-Barbera, J.P., Heikenwalder, M., Withers, D.J., Gil, J., 2019. Cardiac glycosides are broad-spectrum senolytics. Nature Metabolism 1(11), 1074-1088.

Guo, J., Tang, S., Miao, Y., Ge, L., Xu, J., Zeng, X., 2021. The anti-inflammatory effects of lignan glycosides from Cistanche tubulosa stems on LPS/IFN-γ-induced RAW264. 7 macrophage cells via PI3K/AKT pathway. Current Pharmaceutical Biotechnology 22(10), 1380-1391.

Hallböök, H., Felth, J., Eriksson, A., Fryknäs, M., Bohlin, L., Larsson, R., Gullbo, J., 2011. Ex vivo activity of cardiac glycosides in acute leukaemia. PloS one 6(1), e15718.

Hallek, M., Al-Sawaf, O., 2021. Chronic lymphocytic leukemia: 2022 update on diagnostic and therapeutic procedures. American Journal of Hematology 96(12), 1679-1705.

Haux, J., 1999. Digitoxin is a potential anticancer agent for several types of cancer. Medical hypotheses 53(6), 543-548.

Haux, J., Lain, M., Marthinsen, A., Strickert, T., Lundgren, S., 1999. Digitoxin, in non toxic concentrations, induces apoptotic cell death in Jurkat T cells in vitro. ZEITSCHRIFT FUR ONKOLOGIE 31, 14-14.

Hayes, M.R., Pietruszka, J., 2017. Synthesis of glycosides by glycosynthases. Molecules 22(9), 1434.

Hopia, A., Heinonen, M., 1999. Antioxidant activity of flavonol aglycones and their glycosides in methyl linoleate. Journal of the American Oil Chemists' Society 76(1), 139-144.

Houshmand, M., Simonetti, G., Circosta, P., Gaidano, V., Cignetti, A., Martinelli, G., Saglio, G., Gale, R.P., 2019. Chronic myeloid leukemia stem cells. Leukemia 33(7), 1543-1556.

Hsieh, Y.-C., Kirschner, K., Copland, M., 2021. Improving outcomes in chronic myeloid leukemia through harnessing the immunological landscape. Leukemia 35(5), 1229-1242.

Hutt, D., 2018. Engraftment, graft failure, and rejection. The European Blood and Marrow Transplantation Textbook for Nurses, 259-270.

Ikeda, T., Tsumagari, H., Honbu, T., Nohara, T., 2003. Cytotoxic activity of steroidal glycosides from solanum plants. Biological and Pharmaceutical Bulletin 26(8), 1198-1201.

Iskierka-Jażdżewska, E., Obracaj, A., Urbaniak, M., Robak, T., 2022. New Treatment Options for Newly-Diagnosed and Relapsed Chronic Lymphocytic Leukemia. Current Treatment Options in Oncology 23(6), 775-795.

Jabbour, E., Thomas, D., Cortes, J., Kantarjian, H.M., O'Brien, S., 2010. Central nervous system prophylaxis in adults with acute lymphoblastic leukemia. Cancer 116(10), 2290-2300.

Jain, P., Korula, A., Deshpande, P., Pn, N., Abu Alex, A., Abraham, A., Srivastava, A., Janet, N.B., Lakshmi, K.M., Balasubramanian, P., George, B., Mathews, V., 2018. Adult Acute Lymphoblastic Leukemia: Limitations of Intensification of Therapy in a Developing Country. Journal of Global Oncology(4), 1-12.

Jeong, E.J., Kim, T.B., Yang, H., Kang, S.Y., Kim, S.Y., Sung, S.H., Kim, Y.C., 2012. Neuroprotective iridoid glycosides from Cornus officinalis fruits against glutamate-induced toxicity in HT22 hippocampal cells. Phytomedicine 19(3-4), 317-321.

Jones, J.A., Byrd, J.C., 2014. How will B-cell-receptor–targeted therapies change future CLL therapy? Blood, The Journal of the American Society of Hematology 123(10), 1455-1460.

Kayser, S., Levis, M.J., 2014. FLT3 tyrosine kinase inhibitors in acute myeloid leukemia: clinical implications and limitations. Leukemia & Lymphoma 55(2), 243-255.

Khan, H., Pervaiz, A., Intagliata, S., Das, N., Nagulapalli Venkata, K.C., Atanasov, A.G., Najda, A., Nabavi, S.M., Wang, D., Pittalà, V., Bishayee, A., 2020. The analgesic potential of glycosides derived from medicinal plants. DARU Journal of Pharmaceutical Sciences 28(1), 387-401.

Khan, M., Taft, B., Rasku, M., Laber, D., Chesney, J., Miller, D., 2007. A phase II trial of biochemotherapy with cisplatin, vinblastine, dacarbazine, interleukin-2, interferon, and digoxin in melanoma matients. Journal of Clinical Oncology 25(18_suppl), 8573-8573.

Khattak, S., Khan, H., 2018. Phyto-glycosides as therapeutic target in the treatment of diabetes. Mini Reviews in Medicinal Chemistry 18(3), 208-215.

Khazdair, M.R., Anaeigoudari, A., Hashemzehi, M., Mohebbati, R., 2019. Neuroprotective potency of some spice herbs, a literature review. Journal of Traditional and Complementary Medicine 9(2), 98-105.

KUMAR, J.S., KUMAR, J.N., Kar, R., Ambasta, R.K., Kumar, P., 2015. p38 MAPK and PI3K/AKT signalling cascades in Parkinson's disease.

Kumavath, R., Paul, S., Pavithran, H., Paul, M.K., Ghosh, P., Barh, D., Azevedo, V., 2021. Emergence of cardiac glycosides as potential drugs: Current and future scope for cancer therapeutics. Biomolecules 11(9), 1275.

Kurek, J.M., Krejpcio, Z., 2019. The functional and health-promoting properties of Stevia rebaudiana Bertoni and its glycosides with special focus on the antidiabetic potential – A review. Journal of Functional Foods 61, 103465.

Kurtin, S.E., 2021. Optimizing Treatment of Chronic Lymphocytic Leukemia. Journal of the advanced practitioner in oncology 12(3), 325-328.

Lai, R., Hirsch-Ginsberg, C.F., Bueso-Ramos, C., 2000. Pathologic diagnosis of acute lymphocytic leukemia. Hematology/oncology clinics of North America 14(6), 1209-1235.

Larsson, R., Kristensen, J., Sandberg, C., Nygren, P., 1992. Laboratory determination of chemotherapeutic drug resistance in tumor cells from patients with leukemia, using a fluorometric microculture cytotoxicity assay (FMCA). International journal of cancer 50(2), 177-185.

Laverdière, I., Boileau, M., Neumann, A.L., Frison, H., Mitchell, A., Ng, S.W., Wang, J.C., Minden, M.D., Eppert, K., 2018. Leukemic stem cell signatures identify novel therapeutics targeting acute myeloid leukemia. Blood cancer journal 8(6), 1-16.

Lee, S.M.Y., Li, M.L.Y., Tse, Y.C., Leung, S.C.L., Lee, M.M.S., Tsui, S.K.W., Fung, K.P., Lee, C.Y., Waye, M.M.Y., 2002. Paeoniae Radix, a Chinese herbal extract, inhibit hepatoma cells growth by inducing apoptosis in a p53 independent pathway. Life sciences 71(19), 2267-2277.

Linn, Y.H., Ei, W.W., Myint, L.M.M., Lwin, K.M., 2021. Anti-hepatitis B activities of Myanmar medicinal plants: a narrative review of current evidence. VirusDisease 32(3), 446-466.

Liu, M., Kong, J.-Q., 2018. The enzymatic biosynthesis of acylated steroidal glycosides

and their cytotoxic activity. Acta pharmaceutica sinica B 8(6), 981-994.
Liu, X., Li, Y., Wang, K., Chen, Y., Shi, M., Zhang, X., Pan, W., Li, N., Tang, B., 2021. GSH-responsive nanoprodrug to inhibit glycolysis and alleviate immunosuppression for cancer therapy. Nano Letters 21(18), 7862-7869.
Lowenberg, B., Downing, J.R., Burnett, A., 1999. Acute myeloid leukemia. New England Journal of Medicine 341(14), 1051-1062.
Lu, Q., He, Y., Wang, Y., Gao, L., Zheng, Y., Zhang, Z., Cao, B., Wang, Q., Mao, X., Hu, S., 2018. Saponins from Paris forrestii (Takht.) H. Li display potent activity against acute myeloid leukemia by suppressing the RNF6/AKT/mTOR signaling pathway. Frontiers in Pharmacology 9, 673.
Matsuda, H., Morikawa, T., Ando, S., Toguchida, I., Yoshikawa, M., 2003. Structural requirements of flavonoids for nitric oxide production inhibitory activity and mechanism of action. Bioorganic & medicinal chemistry 11(9), 1995-2000.
Maucher, M., Srour, M., Danhof, S., Einsele, H., Hudecek, M., Yakoub-Agha, I., 2021. Current limitations and perspectives of chimeric antigen receptor-T-cells in acute myeloid leukemia. Cancers 13(24), 6157.
Mekhail, T., Kaur, H., Ganapathi, R., Budd, G.T., Elson, P., Bukowski, R.M., 2006. Phase 1 trial of Anvirzel™ in patients with refractory solid tumors. Investigational new drugs 24(5), 423-427.
Ml Hossion, A., Sasaki, K., 2013. Novel quercetin glycosides as potent anti-MRSA and anti-VRE agents. Recent patents on anti-infective drug discovery 8(3), 198-205.
Mojtahedi, H., Yazdanpanah, N., Rezaei, N., 2021. Chronic myeloid leukemia stem cells: targeting therapeutic implications. Stem Cell Research & Therapy 12(1), 603.
Music, M., Prassas, I., Diamandis, E.P., 2018. Optimizing cancer immunotherapy: Is it time for personalized predictive biomarkers? Critical Reviews in Clinical Laboratory Sciences 55(7), 466-479.
Naumovski, L., Morgan, R., Hecht, F., Link, M.P., Glader, B.E., Smith, S.D., 1988. Philadelphia chromosome-positive acute lymphoblastic leukemia cell lines without classical breakpoint cluster region rearrangement. Cancer research 48(10), 2876-2879.
Newman, R.A., Yang, P., Pawlus, A.D., Block, K.I., 2008. Cardiac glycosides as novel cancer therapeutic agents. Molecular interventions 8(1), 36.
Nijmeijer, B.A., van Schie, M.L.J., Verzaal, P., Willemze, R., Falkenburg, J.H.F., 2005. Responses to donor lymphocyte infusion for acute lymphoblastic leukemia may be determined by both qualitative and quantitative limitations of antileukemic T-cell responses as observed in an animal model for human leukemia. Experimental Hematology 33(10), 1172-1181.
O'Brien, S.M., Kantarjian, H.M., Thomas, D.A., Cortes, J., Giles, F.J., Wierda, W.G., Koller, C.A., Ferrajoli, A., Browning, M., Lerner, S., 2003. Alemtuzumab as treatment for residual disease after chemotherapy in patients with chronic lymphocytic leukemia. Cancer 98(12), 2657-2663.
Onaolapo, A.Y., Onaolapo, O.J., 2019. 9 - Herbal Beverages and Brain Function in Health and Disease, in: Grumezescu, A.M., Holban, A.M. (Eds.), Functional and Medicinal Beverages. Academic Press, pp. 313-349.
Parisi, E., Draznin, J., Stoopler, E., Schuster, S.J., Porter, D., Sollecito, T.P., 2002. Acute myelogenous leukemia: Advances and limitations of treatment. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology 93(3), 257-263.
Phromnoi, K., Yodkeeree, S., Anuchapreeda, S., Limtrakul, P., 2009. Inhibition of MMP-3 activity and invasion of the MDA-MB-231 human invasive breast carcinoma cell line by bioflavonoids. Acta Pharmacologica Sinica 30(8), 1169-1176.
Prassas, I., Diamandis, E.P., 2008. Novel therapeutic applications of cardiac glycosides. Nature reviews Drug discovery 7(11), 926-935.
Puckett, Y., Chan, O., 2022. Acute lymphocytic leukemia, StatPearls [Internet]. StatPearls Publishing.
Qasim, W., 2019. Allogeneic CAR T cell therapies for leukemia. American journal of hematology 94(S1), S50-S54.
Ravandi, F., Walter, R.B., Freeman, S.D., 2018. Evaluating measurable residual disease in acute myeloid leukemia. Blood advances 2(11), 1356-1366.
Reddy, D., Kumavath, R., Barh, D., Azevedo, V., Ghosh, P., 2020. Anticancer and antiviral properties of cardiac glycosides: A review to explore the mechanism of actions. Molecules 25(16), 3596.
Ross, J.S., Schenkein, D.P., Pietrusko, R., Rolfe, M., Linette, G.P., Stec, J., Stagliano, N.E., Ginsburg, G.S., Symmans, W.F., Pusztai, L., 2004. Targeted therapies for cancer 2004.

American journal of clinical pathology 122(4), 598-609.

Sadzuka, Y., Hirotsu, S., Hirota, S., 1999. Effective irinotecan (CPT-11)-containing liposomes: intraliposomal conversion to the active metabolite SN-38. Japanese journal of cancer research 90(2), 226-232.

Sato, T., Kawamoto, A., Tamura, A., Tatsumi, Y., Fujii, T., 1992. Mechanism of antioxidant action of pueraria glycoside (PG)-1 (an isoflavonoid) and mangiferin (a xanthonoid). Chemical & pharmaceutical bulletin 40(3), 721-724.

Schmiegelow, K., Müller, K., Mogensen, S.S., Mogensen, P.R., Wolthers, B.O., Stoltze, U.K., Tuckuviene, R., Frandsen, T., 2017. Non-infectious chemotherapy-associated acute toxicities during childhood acute lymphoblastic leukemia therapy. F1000Research 6, 444.

Schoner, W., Scheiner-Bobis, G., 2007. Endogenous and exogenous cardiac glycosides and their mechanisms of action. American journal of cardiovascular drugs 7, 173-189.

She, Y., Shao, L., Zhang, Y., Hao, Y., Cai, Y., Cheng, Z., Deng, C., Liu, X., 2019. Neuroprotective effect of glycosides in Buyang Huanwu Decoction on pyroptosis following cerebral ischemia-reperfusion injury in rats. Journal of Ethnopharmacology 242, 112051.

Shibata, A., Nagaya, T., Imai, T., Funahashi, H., Nakao, A., Seo, H., 2002. Inhibition of NF-κB activity decreases the VEGF mRNA expression in MDA-MB-231 breast cancer cells. Breast cancer research and treatment 73(3), 237-243.

Soto-Blanco, B., 2022. Chapter 12 - Herbal glycosides in healthcare, in: Mandal, S.C., Nayak, A.K., Dhara, A.K. (Eds.), Herbal Biomolecules in Healthcare Applications. Academic Press, pp. 239-282.

Sreenivasan, Y., Raghavendra, P.B., Manna, S.K., 2006. RETRACTED ARTICLE: Oleandrin-Mediated Expression of Fas Potentiates Apoptosis in Tumor Cells. Journal of clinical immunology 26(4), 308-322.

Sun, H., Luo, G., Chen, D., Xiang, Z., 2016. A comprehensive and system review for the pharmacological mechanism of action of rhein, an active anthraquinone ingredient. Frontiers in pharmacology 7, 247.

Tagousop, C.N., Tamokou, J.-d.-D., Ekom, S.E., Ngnokam, D., Voutquenne-Nazabadioko, L., 2018. Antimicrobial activities of flavonoid glycosides from Graptophyllum grandulosum and their mechanism of antibacterial action. BMC complementary and alternative medicine 18(1), 1-10.

Tailler, M., Senovilla, L., Lainey, E., Thepot, S., Metivier, D., Sebert, M., Baud, V., Billot, K., Fenaux, P., Galluzzi, L., 2012. Antineoplastic activity of ouabain and pyrithione zinc in acute myeloid leukemia. Oncogene 31(30), 3536-3546.

Talpaz, M., McCredie, K.B., Mavligit, G.M., Gutterman, J.U., 1983. Leukocyte interferon-induced myeloid cytoreduction in chronic myelogenous leukemia.

Torkaman, A., Charkari, N.M., Aghaeipour, M., 2011. An approach for leukemia classification based on cooperative game theory. Analytical Cellular Pathology 34(5), 235-246.

Trinh, C., 2020. Effects of Molecular Dynamics on the Electrostatic Interactions between Bcr-Abl Kinase and the Chronic Myeloid Leukemia Drug Imatinib: A Computational Study.

Uras, I.Z., Sexl, V., Kollmann, K., 2020. CDK6 inhibition: A novel approach in AML management. International Journal of Molecular Sciences 21(7), 2528.

Van Driessche, A., Gao, L., Stauss, H.J., Ponsaerts, P., Van Bockstaele, D.R., Berneman, Z.N., Van Tendeloo, V.F.I., 2005. Antigen-specific cellular immunotherapy of leukemia. Leukemia 19(11), 1863-1871.

Vener, C., Banzi, R., Ambrogi, F., Ferrero, A., Saglio, G., Pravettoni, G., Sant, M., 2020. First-line imatinib vs second-and third-generation TKIs for chronic-phase CML: a systematic review and meta-analysis. Blood advances 4(12), 2723-2735.

Wang, J.K.T., Portbury, S., Thomas, M.B., Barney, S., Ricca, D.J., Morris, D.L., Warner, D.S., Lo, D.C., 2006. Cardiac glycosides provide neuroprotection against ischemic stroke: discovery by a brain slice-based compound screening platform. Proceedings of the National Academy of Sciences of the United States of America 103(27), 10461-10466.

Weil, M., Jacobson, M., Coles, H., Davies, T., Gardner, R., Raff, K., Raff, M., 1996. Constitutive expression of the machinery for programmed cell death. The Journal of Cell Biology 133(5), 1053-1059.

Winnicka, K., Bielawski, K., Bielawska, A., 2006. Cardiac glycosides in cancer research and cancer therapy. Acta Pol Pharm 63(2), 109-115.

Xu, H.-Y., Chen, Z.-W., Wu, Y.-M., 2012. Antitumor activity of total paeony glycoside against human chronic myelocytic leukemia K562 cell lines in vitro and in vivo. Medical Oncology 29(2), 1137-1147.

Ya-Zheng, Z., Zhang, Y.-Y., Han, H., Rui-Ping, F., Yang, H., Zhong, L., Jun-Ping, K., Bo-Yang, Y., 2018. Advances in the antitumor activities and mechanisms of action of steroidal saponins. Chinese journal of natural medicines 16(10), 732-748.

Yang, B., Liu, H., Yang, J., Gupta, V.K., Jiang, Y., 2018. New insights on bioactivities and biosynthesis of flavonoid glycosides. Trends in food science & technology 79, 116-124.

Yanir, A.D., Martinez, C.A., Sasa, G., Leung, K., Gottschalk, S., Omer, B., Ahmed, N., Hegde, M., Eunji, J., Liu, H., 2018. Current allogeneic hematopoietic stem cell transplantation for pediatric acute lymphocytic leukemia: success, failure and future perspectives—a single-center experience, 2008 to 2016. Biology of Blood and Marrow Transplantation 24(7), 1424-1431.

Yun, S.-H., Shin, S.-W., Stonik, V.A., Park, J.-I., 2016. Ceramide as a target of marine triterpene glycosides for treatment of human myeloid leukemia. Marine Drugs 14(11), 205.

Yusuf, M.A., Singh, B.N., Sudheer, S., Kharwar, R.N., Siddiqui, S., Abdel-Azeem, A.M., Fernandes Fraceto, L., Dashora, K., Gupta, V.K., 2019. Chrysophanol: a natural anthraquinone with multifaceted biotherapeutic potential. Biomolecules 9(2), 68.

Zhang, W., Yamada, H., Sakai, N., Niikawa, S., Nozawa, Y., 1992. Enhancement of radiosensitivity by tamoxifen in C6 glioma cells. Neurosurgery 31(4), 725-730.

Zhang, X.H., Wang, X.Y., Zhou, Z.W., Bai, H., Shi, L., Yang, Y.X., Zhou, S.F., Zhang, X.C., 2017. The combination of digoxin and GSK2606414 exerts synergistic anticancer activity against leukemia in vitro and in vivo. Biofactors 43(6), 812-820.

Zhao, Z.-M., Sun, Z.-H., Chen, M.-H., Liao, Q., Tan, M., Zhang, X.-W., Zhu, H.-D., Pi, R.-B., Yin, S., 2013. Neuroprotective polyhydroxypregnane glycosides from Cynanchum otophyllum. Steroids 78(10), 1015-1020.