Artificial Intelligence Applications And Innovations Vol. 1 No. 1 (2024)

Article history:
Received 02 September 2023
Revised 05 November 2023
Accepted 13 November 2023
Published online 01 January 2024

Trending Drugs Combination to Target Leukemia associated Proteins/Genes: using Graph Neural Networks under the RAIN Protocol

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A r t i c l e I n f o

Article type:
Original Research

How to cite this article:
Kiyaee, A.A., & Tabatabaei, S.G.H. (2024). Trending Drugs Combination to Target Leukemia associated Proteins/Genes: using Graph Neural Networks under the RAIN Protocol. Artificial Intelligence Applications and Innovations, *1*(1), 42-65.
https://doi.org/10.61838/jaiai.1.1.4

A B S T R A C T

Leukemia is a cancer that impacts the tissues responsible for forming blood in the body, such as the bone marrow and lymphatic system. The treatment approach for leukemia is multifaceted and is determined by factors such as the specific type of leukemia. The care plan for a patient with leukemia should prioritize comfort, reduce the negative effects of chemotherapy, preserve veins, address complications, and offer education and emotional support. This paper examines existing research on combinations of medications for Leukemia. Administering a combination of drugs may reduce the likelihood of a tumour developing resistance to the treatment. Utilizing multiple drugs simultaneously enables the administration of all medications as early as possible in the course of the disease, rather than delaying. To recommend a drug combination to treat/manage Leukemia, under first step of RAIN protocol, we have searched articles including related trend drugs using Natural Language Processing. In the second step, we have employed Graph Neural Network to pass information between these trending drugs and genes that act as potential targets for Leukemia. As a result, the Graph Neural network recommends combining Tretinoin, Asparaginase, and Cytarabine. The network meta-analysis confirmed the effectiveness of these drugs on associated genes. The p-value between leukemia and the scenario that includes combinations of the mentioned drugs is almost zero, indicating an improvement in leukemia treatment. Reviews of clinical trials on these medications support this claim.

Keywords: *Drug Combination, Network Meta-analysis, Graph Neural network, Leukemia.*

1. Introduction

The introduction of the article is divided into two subsections. The first subsection discusses certain genes or proteins that have been identified as potential targets for the treatment of leukemia. The second subsection provides information about drugs that are currently used to treat leukemia. These drugs may target the genes or proteins

mentioned in the first subsection, or they may work through other mechanisms to help fight the disease.

1.1. Associated genes/Proteins

PML (Promyelocytic Leukemia) is a protein that plays a role in the development of Acute Promyelocytic Leukemia (APL) when it merges with the RARα (Retinoic Acid Receptor alpha) protein. The resulting fusion protein, PML-RARα, accounts for over 95% of fusion proteins in APL patients and presents a potential target for treatment. An atlas of direct targets for PML/RARα redefines transcriptional deregulation in APL and offers insight into potential targeted therapies for APL. These therapies include all-trans retinoic acid (ATRA) and arsenic trioxide (As2O3), both of which target the PML-RARα fusion protein for degradation. ATRA stimulates transcription of RARα-target genes to overcome the differentiation block, while As2O3 induces oxidant stress and binds directly to PML, causing partial differentiation and apoptosis of APL cells and more effectively eliminating leukemia-initiating cells [1-3].

Leukemia inhibitory factor (LIF) and its receptor (LIFR) are frequently over-expressed in numerous solid cancers, including leukemia. Recent research has identified the LIF/LIFR axis as a potential clinical target for cancer treatment. LIF/LIFR activate cancer-causing signaling pathways, including JAK/STAT3 as immediate effectors and MAPK, AKT, and mTOR further downstream [4-6].

KMT2A, previously referred to as MLL, is a gene that codes for the histone lysine-specific N-methyltransferase 2A and is situated on chromosome 11q23. KMT2A is commonly targeted by recurrent translocations in acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), or mixed lineage (biphenotypic) leukemia (MLL) [7-9].

RUNX1 is commonly affected by chromosomal and genetic changes in leukemia. Inherited mutations and somatic changes are often linked to acute myeloid leukemia (AML), with RUNX1 mutations indicating a poor prognosis. As a result, RUNX1 represents a potential innovative and intriguing therapeutic target. Several strategies are being developed to target RUNX1 in AML, including the creation of small molecules that target the RUNX1-RUNX1T1 protein, the use of tyrosine kinase inhibitors such as dasatinib and FLT3 inhibitors to target mutations that provide a proliferative advantage to leukemic cells, and experimentation with epigenetic therapies [10, 11].

Roughly 30% of patients with newly diagnosed acute myeloid leukemia (AML) have mutations in the fms-like tyrosine kinase 3 (FLT3) gene. Current guidelines advise swift molecular testing for FLT3 mutations at diagnosis and the early incorporation of targeted agents to achieve deeper remissions and prompt consideration for allogeneic stem cell transplant (ASCT). The approval of the multi-kinase FLT3 inhibitor (FLT3i) midostaurin for use with induction therapy in newly diagnosed FLT3 mutated AML, as well as the more specific and potent FLT3i gilteritinib as a monotherapy for relapsed/refractory (R/R) FLT3 mutated AML, has improved outcomes for patients with FLT3 mutated AML [12, 13].

Chronic myelogenous leukemia (CML) is a myeloproliferative neoplasm that originates in a pluripotent bone marrow stem cell and is consistently associated with the BCR-ABL1 fusion gene. This genetic abnormality results from translocation of ABL1 on chromosome 9 to the region of the BCR gene on chromosome 22. The BCR-ABL1 fusion gene causes aberrant kinase activity and uncontrolled cell proliferation, and is the hallmark of CML. The development of tyrosine kinase inhibitors (TKI) that target the BCR-ABL oncoprotein has led to dramatic improvement in CML management [14-16].

BCR-ABL is an abnormal gene found in chronic myeloid leukemia (CML) cells. This gene makes a protein, BCR-ABL, which causes CML cells to grow and reproduce out of control. BCR-ABL is a type of protein known as a tyrosine kinase. Drugs known as tyrosine kinase inhibitors (TKIs) that target BCR-ABL are the standard treatment for CML [17-19].

CD19 is a protein that is widely expressed on B-cell acute lymphoblastic leukemia (B-ALL) cells. Chimeric antigen receptor (CAR) T-cells targeting CD19 have demonstrated remarkable efficacy in treating B-ALL, inducing complete remissions of disease in up to 90% of patients with relapsed or refractory B-ALL [20-23].

CD34 is a hematopoietic stem cell marker that has been associated with a poorer prognosis in patients with myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML). CD34+CD38− cells have been shown to be able to initiate AML and B-ALL in immunodeficient recipients [23-25].

The MECOM gene, also known as the MDS1 and EVI1 Complex Locus, is located on chromosome 3q26.2. This gene has been extensively studied for its role in maintaining and replicating normal hematopoietic stem cells, as well as

its role as an oncogene when aberrantly expressed. Translocations involving the MECOM gene at 3q26.2 are well-documented and characterized in myeloid disorders, including acute myeloid leukemia (AML), myelodysplastic syndromes (MDS), and chronic myelogenous leukemia (CML), and are associated with a poor prognosis [26-28].

CSF3R is the receptor for colony-stimulating factor 3 (CSF3) and is thought to play a prominent role in the growth and differentiation of granulocytes. CSF3R mutations have been described in patients with severe congenital neutropenia, which can evolve into acute myeloid leukemia (AML) [29, 30].

ZBTB16 is a gene that has been implicated in leukemia. A rare translocation involving the ZBTB16 gene and the RARA gene has been found in some cases of acute myeloid leukemia (AML). This translocation results in the formation of an oncogenic fusion protein, ZBTB16-RARA, which is thought to play a role in the development of AML [31-33].

MEIS1 is a gene that has been implicated in leukemia. It is a transcription factor that is critical for leukemia cell survival and has been shown to be an attractive molecular therapeutic target for leukemias that express this transcription factor. Silencing of MEIS1 in leukemia has been shown to decrease cell growth, induce apoptosis, and delay the development of overt leukemia in vivo [34, 35].

HOXA9 is a homeodomain-containing transcription factor that plays an important role in hematopoietic stem cell expansion and is commonly deregulated in acute leukemias. A variety of upstream genetic alterations in acute myeloid leukemia (AML) lead to overexpression of HOXA9, which is a strong predictor of poor prognosis. In many cases, HOXA9 has been shown to be necessary for maintaining leukemic transformation; however, the molecular mechanisms through which it promotes leukemogenesis remain elusive [36].

BCL2 is a gene that has been implicated in leukemia. Overexpression of BCL2 proteins in acute myeloid leukemia can circumvent resistance to apoptosis and chemotherapy. Considering this effect, the exploration of anti-apoptotic BCL2 inhibitors is considered to have tremendous potential for the discovery of novel pharmacological modulators in cancer. Researchers from the University of Rochester have identified BCL2 inhibitors as potential leukemia stem cell (LSC)-targeting agents due to the role of BCL2 in promoting LSC metabolic homeostasis, demonstrating that two such inhibitors killed inactive and metabolically slower leukemia stem cells [37-39].

DOT1L is a histone methyltransferase that specifically targets nucleosomal histone H3 lysine 79 (H3K79) for mono-, di-, or trimethylation (H3K79me1, me2, or me3). DOT1L is involved in MLL fusion-driven leukemogenesis. Recently, DOT1L has become an attractive therapeutic target for MLL-rearranged leukemias. Rigorous studies have been performed, and much progress has been achieved. Moreover, one DOT1L inhibitor, EPZ-5676, has entered clinical trials [40-42].

WT1 is a leukemia associated antigen (LAA) that is differentially expressed by leukemic blasts. Thus, WT1 may constitute a target for therapies such as those mediated by adoptive-specific T lymphocytes. Limited tissue expression of WT1 in adults suggests that WT1 can be a target for leukemia therapy [43, 44].

MYC is a proto-oncogene that is closely involved in many cancers, including leukemia and lymphoma. In hematological malignancies, aberrant expression of MYC protein results in an uncontrolled rate of proliferation and, thereby, a blockade of the differentiation process. Data in leukemia-derived cells and in animal models of lymphomagenesis and leukemogenesis suggest that MYC would be a good therapeutic target. Several MYC-directed therapies have been assayed in preclinical settings and even in clinical trials [45-47].

MLL is a target of chromosomal translocations in acute leukemias with poor prognosis. The common MLL fusion partner AF9 (MLLT3) can directly bind to AF4, DOT1L, BCOR, and CBX8. Loss of direct BCOR/MLL-AF9 binding causes partial differentiation and increased proliferation. Strikingly, loss of MLL-AF9/BCOR binding abrogated its leukemogenic potential in a mouse model [48, 49].

NPM1 is a nucleus-cytoplasmic shuttling protein which is predominantly located in the nucleolus and exerts multiple functions, including regulation of centrosome duplication, ribosome biogenesis and export, histone assembly, maintenance of genomic stability and response to nucleolar stress. NPM1 mutations are the most common genetic alteration in acute myeloid leukemia (AML), detected in about 30–35% of adult AML and more than 50% of AML with normal karyotype. It is reported that dysfunctional NPM1 might cause AML pathogenesis via its role as a protein chaperone, inhibiting differentiation of leukemia stem cells and regulation of non-coding RNAs. Besides conventional chemotherapies, NPM1 is a promising therapeutic target against AML that warrants further investigation [50, 51].

Rearrangements of the MLLT10 gene occur in acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL), most commonly T-lineage ALL (T-ALL), in patients of all ages. MLLT10 rearranged (MLLT10r) acute leukemia presents a complex diagnostic and therapeutic challenge due to frequent presentation of immature or mixed phenotype, and a lack of consensus regarding optimal therapy. Cases of MLLT10r AML or T-ALL bearing immature phenotype are at high risk of poor outcome, but the underlying molecular mechanisms and sensitivity to targeted therapies remain poorly characterized. Understanding the underlying genomics of MLLT10r acute leukemia, both clinically and molecularly, will improve prognostic stratification and accelerate the development of targeted therapeutic strategies, to improve patient outcomes [52, 53].

TAL1 (T-cell acute leukemia protein 1) is a transcription factor that is involved in the process of hematopoiesis and leukemogenesis. During definitive hematopoiesis, TAL1 is required for erythroid differentiation, yet it is epigenetically repressed during human thymopoiesis. Oncogenic events leading to the ectopic expression of TAL1 in the T-cell lineage are considered strong drivers of T-cell leukemogenesis [54, 55].

IL11 receptor (IL11R) is a suitable cell surface target for ligand-directed applications in human leukemia and lymphoma. A targeted peptidomimetic prototype (termed BMTP-11), specifically bound to leukemia and lymphoma cell membranes, induced ligand–receptor internalization mediated by the IL11R, and resulted in a specific dose-dependent cell death induction in these cells. These results indicate that BMTP-11 and its derivatives have translational potential against this group of malignant diseases [56].

IL3 receptor (CD123) has been demonstrated to be expressed on CD34+CD38- leukemic stem cells in AML and CML. It has been shown to be an effective therapeutic target in pre-clinical AML models. These data indicate that the IL3 receptor is highly expressed on CD34+38- Bcr-Abl (+) CML stem cells and represents an exciting new and feasible target for therapeutic intervention. Moreover, DT-IL3 conjugates represent a novel therapeutic modality for selective targeting of highly resistant CML stem cells [57, 58].

CSF2, also known as GM-CSF, is a cytokine that regulates various cellular processes including differentiation, proliferation, survival, and leukocyte activation. The receptor for GM-CSF is composed of the CSF2RA and CSF2RB receptor subunits. CSF2RB is also a shared common beta subunit for the IL3 and IL5 receptors, and is the predominant subunit for signaling. CSF2RA is primarily a ligand-binding subunit. It has been reported that GM-CSF signaling is inhibitory to leukemogenesis in a murine model for t (8;21) acute myeloid leukemia (AML), and aids in promoting myeloid differentiation of leukemic blasts [30, 57].

RARA is a gene that has been associated with acute myeloid leukemia (AML). Researchers have identified specific super enhancers (SE) -- regions of DNA that drive the over production of certain gene products -- in cells from children with AML. One SE of specific interest was associated with the gene RARA. Sixty-four percent of the pediatric patient AML samples the researchers studied had this RARA SE. AML cells with a RARA SE were sensitive to treatment with the drug tamibarotene in lab cultures and in animal models, prolonging survival and reducing the leukemia burden [31, 59].

JAK2 (Janus kinase 2) is a protein tyrosine kinase involved in cytokine receptor signaling. Mutations in JAK2 have been identified in acute lymphoblastic leukemia (ALL) and other hematologic malignancies. JAK2 mutations might be closely correlated with acute leukemia formation, treatment and prognosis. JAK2 and STAT5 have been described as potential therapeutic targets in leukemic stem cells (LSCs) in chronic myeloid leukemia (CML) [60-62].

CD22 is a B-lineage differentiation antigen that has emerged as a leading therapeutic target in acute lymphoblastic leukemia (ALL). CD22 is among the most frequently expressed surface antigens in B-precursor ALL. This antigen is expressed on immature and mature B cells but not on haemopoietic stem cells and, therefore, is an ideal target for immunotherapy. These characteristics make CD22 an excellent potential therapeutic target in patients with relapsed and chemotherapy-refractory ALL [63, 64].

RUNX1 is a frequent target of chromosomal and genetic alterations in leukemia. Chromosomal rearrangements involving RUNX1 or CBFβ, somatic point mutations in RUNX1, and amplification of RUNX1 have all been described in acute leukemia. Germline mutations and somatic alterations are frequently associated with acute myeloid leukemia (AML) with RUNX1 mutations conferring unfavorable prognosis. Therefore, RUNX1 constitutes a potential innovative and interesting therapeutic target. Potential approaches include the development of small molecules targeting the RUNX1-RUNX1T1 protein, the use of tyrosine kinase inhibitors such as dasatinib and FLT3 inhibitors to target mutations that lead to a

proliferative advantage of the leukemic cells, and experimentation with epigenetic therapies [65].

BMI1, a Polycomb-group gene located at 10p12.2, is implicated in the pathogenesis of a variety of tumors. It is recurrently targeted by chromosomal aberrations in B-cell leukemia/lymphoma. BMI1 has also been implicated in the maintenance of the proliferative capacity of leukemic stem cells (LSCs). Targeting BMI-1, which markedly increased in the leukemic cells, was associated with marked decrease in leukemic burden [66-68].

1.2. Leukemia treatments

Cytarabine is an important drug in the treatment of acute myeloid leukemia (AML). It is used in induction therapy in combination with anthracyclines and in consolidation therapy at higher doses for AML patients[1]. The combination of cytarabine with purine nucleoside analogs, such as fludarabine and cladribine, has been extensively explored in the treatment of patients with relapsed or refractory AML. In recent years, there has been a significant shift toward the use of novel and effective, target-directed therapies, including inhibitors of mutant FMS-like tyrosine kinase 3 (FLT3) and isocitrate dehydrogenase (IDH), the B-cell lymphoma 2 inhibitor venetoclax, and the hedgehog pathway inhibitor glasdegib[2]. In older patients, the combination of a hypomethylating agent or low-dose cytarabine with venetoclax achieved composite response rates that approximate those seen with standard induction regimens in similar populations, but with potentially less toxicity and early mortality [69-71].

Daunorubicin is an anthracycline drug that has been used in combination with cytarabine as a standard induction therapy for adult patients with acute myeloid leukemia (AML) for more than four decades[5]. This combination is also known as the "3+7 regimen" (3 days of daunorubicin + 7 days of cytarabine). Recently, a phase 2 trial investigated the activity and safety of venetoclax plus 3+7 daunorubicin and cytarabine chemotherapy in adults with AML. The composite complete remission rate after one cycle of this regimen was 91% [72-74].

Mercaptopurine is a chemotherapy drug mainly used to treat acute lymphoblastic leukemia (ALL). It can also be used to treat acute myeloid leukemia (AML) and acute promyelocytic leukemia (a rare form of AML). It is a purine analogue pro-drug that interferes with nucleotide synthesis and salvage pathways. Maintenance therapy (MT) with oral methotrexate (MTX) and 6-mercaptopurine (6-MP) is essential for the cure of ALL. The primary cytotoxic mechanism involves the incorporation of thioguanine nucleotides (TGNs) into DNA, which may be enhanced by the inhibition of de novo purine synthesis by other MTX/6-MP metabolites [75-77].

Vincristine is a chemotherapy drug that is commonly used in combination with other drugs to treat acute lymphoblastic leukemia (ALL)[3]. It is an antimitotic compound that disrupts microtubule dynamics, arresting the cell cycle. The use of pulse therapy with vincristine and dexamethasone for childhood ALL to determine if this therapy could be safely omitted beyond 1 year of treatment without leading to an inferior outcome in any risk subgroup of childhood ALL [78-80].

Methotrexate is a chemotherapy drug that is used to treat acute lymphoblastic leukemia (ALL). It is an antifolate that exerts its cytotoxicity by depleting reduced folates and directly inhibiting distal steps in nucleotide synthesis, thereby blocking thymidine and de novo purine synthesis. Maintenance therapy (MT) with oral methotrexate (MTX) and 6-mercaptopurine (6-MP) is essential for the cure of ALL. MTX and 6-MP interfere with nucleotide synthesis and salvage pathways. The primary cytotoxic mechanism involves the incorporation of thioguanine nucleotides (TGNs) into DNA, which may be enhanced by the inhibition of de novo purine synthesis by other MTX/6-MP metabolites [81-85].

Busulfan is a chemotherapy drug that is used in combination with other drugs as a conditioning treatment prior to allogeneic marrow transplantation in patients with leukemia. A dose-reduced intravenous busulfan-based regimen in combination with the purine analogue fludarabine is currently a well-established reduced-intensity conditioning regimen for patients with acute myeloid leukemia or myelodysplastic syndrome considered ineligible for myeloablative conditioning treatments [86-90].

Cyclophosphamide is a chemotherapy drug that has been reported to improve the efficacy of patients with acute lymphoblastic leukemia (ALL) and has achieved promising efficacy. However, it is still unclear to evaluate its efficacy and safety for ALL [91, 92].

Doxorubicin is an effective chemotherapy drug for the treatment of acute lymphoblastic leukemia (ALL) in children[4]. Bispecific antibodies (BsAbs) improved the targeting and cytotoxic activity of a clinically approved and low-toxic PEGylated liposomal formulation of doxorubicin (Caelyx) toward leukemia cell lines and patient-derived

samples that are immunophenotypically heterogeneous and representative of high-risk subtypes of childhood leukemia [93-95].

Asparaginase is an enzyme that depletes serum levels of the amino acid L-asparagine. Since leukemic cells are unable to synthesize this amino acid, its deprivation results in cell death[3]. Asparaginase is an important component of acute lymphoblastic leukemia (ALL) treatment. L-asparaginase rewires the biosynthetic and bioenergetic pathways of leukemia cells to activate both anti-leukemic and pro-survival processes [96-98].

Tretinoin, also known as all-trans-retinoic acid (ATRA), is used to induce remission in people with acute promyelocytic leukemia (APL) who have a mutation (the t(15;17) translocation that gives rise to the PML::RARα fusion gene)[5]. It is not used for maintenance therapy. Arsenic trioxide and tretinoin (AsO/ATRA) has been studied for the treatment of APL. It is the preferred induction regimen for newly diagnosed patients with APL who have low-risk disease (white blood cell count [WBC] ≤10,000/mcL), and it is the recommended induction regimen for patients with high-risk disease (WBC >10,000/mcL) who cannot tolerate anthracyclines [99-101].

Imatinib is a selective BCR-ABL1 kinase inhibitor that improved the prognosis for patients with chronic myeloid leukemia (CML). Efficacy and safety analyses on the basis of more than 10 years of follow-up in patients with CML who were treated with imatinib as initial therapy showed that the efficacy of imatinib persisted over time and that long-term administration of imatinib was not associated with unacceptable cumulative or late toxic effects [102, 103].

Idarubicin is an anthracycline drug that is highly effective in the treatment of acute myeloid leukemia (AML). It is active when given orally and can be used to design anti-leukemic regimens that may be given orally and be particularly useful in elderly patients with AML considered unsuitable for standard intensive aggressive treatments [104-106].

Etoposide is an anticancer drug that has been shown to be active as monotherapy in acute myeloid leukemia (AML). However, high doses or long-term etoposide treatment can induce therapy-related leukemia [107, 108].

Thioguanine is an anti-cancer drug used for the treatment of leukemia. A recent study protocol called Thiopurine Enhanced ALL Maintenance (TEAM) aims to evaluate the improvement in disease-free survival by adding very low dose 6-thioguanine to 6-mercaptopurine/methotrexate-based maintenance therapy in pediatric and adult patients (0–45 years) with newly diagnosed B-cell precursor or T-cell acute lymphoblastic leukemia treated according to the intermediate risk-high group of the ALLTogether1 protocol [109-112].

Arsenic trioxide is used in combination with all-trans retinoic acid (ATRA) for the treatment of acute promyelocytic leukemia (APL). This combination has been associated with substantial improvements in outcomes, and APL is now the most curable subtype of acute myeloid leukemia [99, 100, 112, 113].

Fludarabine is an antineoplastic agent used in the treatment of hematological malignancies, particularly chronic lymphocytic leukemia (CLL) and indolent B-cell lymphoma. Because of its immunosuppressive effects, fludarabine has been added to reduced intensity conditioning regimens [27, 114-116].

Amsacrine is an antineoplastic agent that is effective in the treatment of acute leukemias. Amsacrine-based induction therapy in AML patients with cardiac comorbidities was not recommended as a substitute for standard induction [117-120].

Mitoxantrone is an active agent in the treatment of acute leukemia. It has been used in combination with etoposide in studies that included both refractory and relapsed AML patients with reported complete remission (CR) rates ranging from 16% to 61% [107, 121, 122].

Cytosine arabinoside, also known as cytarabine, is an important drug in the treatment of acute myeloid leukemia (AML). It is used in induction therapy in combination with anthracyclines and in consolidation therapy at higher doses for AML patients[3]. High-dose cytarabine (2000 to 3000 mg per square meter of body-surface area) is toxic but results in higher rates of relapse-free survival than does the conventional dose of 100 to 400 mg per square meter [70, 123, 124].

Recombinant Interleukin-3 (IL-3) has been tested for its efficacy in the treatment of leukemia. A novel fusion protein, DT388IL3, composed of the catalytic and translocation domains of diphtheria toxin (DT388) fused with a Met-His linker to human interleukin 3 (IL-3), was tested for anti-leukemia efficacy in an in vivo model of differentiated human acute myeloid leukemia (AML) [125-128].

Transplant conditioning is a crucial part of the leukemia treatment process. Before the transplant, doctors will administer chemotherapy, radiation therapy, or a combination of both to kill as many cancer cells as possible.

This stage of treatment also suppresses the immune system, reducing the likelihood of the body rejecting the transplant, and can make room for new stem cells. Conditioning regimens play an important role in eradicating leukemic cells [129-131].

Myeloablative conditioning is a type of preparative regimen used before a stem cell transplant. The purpose of the preparative regimen is to provide adequate immunosuppression to prevent rejection of the transplanted graft and to eradicate the disease for which the transplant is being performed. Myeloablative conditioning for acute lymphoblastic leukemia (ALL) has generally included total-body irradiation (TBI) or busulfan. Given the ability of TBI-based myeloablative regimens to eradicate the leukemia cells in sanctuary sites, cyclophosphamide and TBI remain the preferred myeloablative regimen for ALL [129, 132, 133].

A preparative regimen, also known as a conditioning regimen, is a critical element in the hematopoietic cell transplant (HCT) procedure. The purpose of the preparative regimen is twofold: to provide adequate immunosuppression to prevent rejection of the transplanted graft and to eradicate the disease for which the transplant is being performed. There are two main types of preparative regimens: standard-intensity regimen and reduced-intensity regimen. A standard-intensity regimen uses high doses of chemotherapy, with or without high doses of radiation. It is also called a myeloablative regimen. A reduced-intensity regimen uses a lower dose of chemotherapy, with or without lower doses of radiation. It is also called a non-myeloablative regimen [134].

Anthracyclines are widely used chemotherapy drugs derived from certain types of Streptomyces bacteria. They are used to treat many types of cancer, including leukemias, lymphomas, and cancers of the breast, stomach, uterus, ovary, and lung, among others. Anthracyclines work by damaging the DNA of cancer cells, which causes them to die before they can multiply. There are several types of anthracyclines used in chemotherapy, with certain drugs proving especially effective in treating specific cancer types [135].

Filgrastim is a medication used to help increase the number of white blood cells, and decrease the length of time with fever in people with acute myeloid leukemia (AML) who are receiving treatment with chemotherapy medications. Filgrastim is approved to reduce the chance of infection in patients with neutropenia caused by some types of chemotherapy, including chemotherapy for acute myeloid leukemia [136].

Prednisolone is a steroid that is used to help destroy leukemia cells or to reduce allergic reactions to some chemotherapy drugs. It is approved to be used to reduce inflammation and suppress the body's immune response. Prednisone has been the glucocorticoid most commonly used in the treatment of patients with acute lymphoblastic leukemia (ALL). It is typically given for 4 consecutive weeks in combination with other chemotherapy drugs [120, 137, 138].

Drugs known as tyrosine kinase inhibitors (TKIs) that target BCR-ABL are the standard treatment for chronic myeloid leukemia (CML). These drugs work by switching off the tyrosine kinase that is made by the BCR-ABL1 gene in the leukemia cells, stopping or slowing the bone marrow from making abnormal white blood cells.

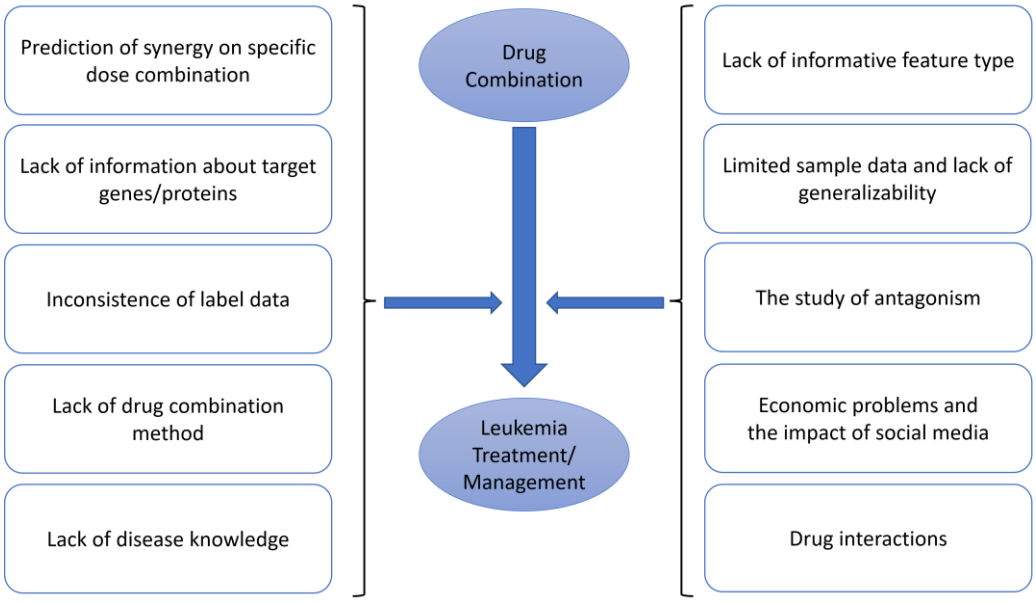


Figure 1

The effects of proposed drug combinations on the management of Leukemia incidents.

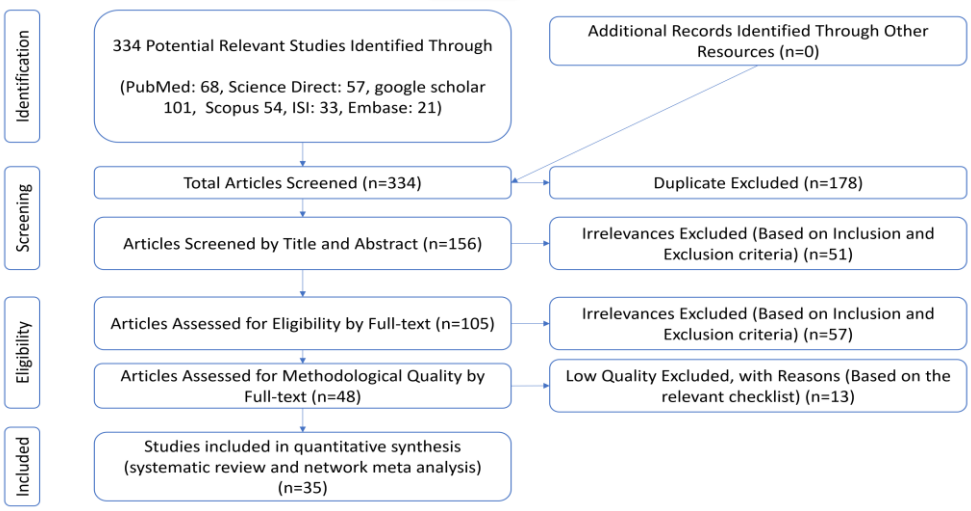


Figure 2

PRISMA (2020) flow diagram indicating the stages of sieving articles in this RAIN protocol.

Some examples of TKIs used to treat CML include Imatinib (Gleevec), Dasatinib (Sprycel), Nilotinib (Tasigna), Bosutinib (Bosulif), Ponatinib (Iclusig), and Asciminib (Scemblix) [15, 17, 139, 140].

Azacitidine is a medication used to treat certain types of leukemia, including acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS). It is designed to slow the production of leukemia cells and help the bone marrow produce more healthy and normal functioning cells. Goals of therapy include increasing blood cell counts, reducing the risk of infection, reducing the amount of blood transfusions needed, and decreasing the risk of bleeding.

Table 1

p-value between scenarios and Leukemia

Scenario	Drug Combinations	p-value
S1	Tretinoin	1.0193E-02
S2	S1 + Asparaginase	8.7631E-05
S3	S2 + Cytarabine	3.4965E-05

Table 2

p-values between Leukemia and human proteins/genes after implementing scenarios

Association Name	S0	S1	S2	S3	Association Name	S0	S1	S2	S3
LIF	2E-06	1	1	1	BCL2	8E-05	1	1	1
PML	2E-06	1	1	1	DOT1L	8E-05	0.97	0.99	1
LIFR	1E-05	0.9	1	1	TXK	8E-05	1	1	1
KMT2A	1E-05	0.99	1	1	WT1	8E-05	1	1	1
EMB	2E-05	0.8	0.8	0.8	NM	8E-05	0.99	0.99	0.99
RUNX1	2E-05	1	1	1	MYC	9E-05	1	1	1
ASPG	2E-05	0	1	1	MLLT3	9E-05	0.92	1	1
FLT3	2E-05	1	1	1	NPM1	9E-05	1	1	1
ASRGL1	3E-05	0	1	1	ERVK-20	1E-04	0	0	0
CD33	3E-05	1	1	1	MRPL28	1E-04	0.99	0.99	1
ABL1	4E-05	0.98	1	1	MLLT10	1E-04	0.68	0.68	0.95
IL6ST	4E-05	0.99	0.99	0.99	ERVK-18	1E-04	0	0	0
OSM	4E-05	0.99	0.99	0.99	TAL1	1E-04	0.98	1	1
LRPPRC	4E-05	0.99	0.99	0.99	ERVW-1	1E-04	0.72	0.72	0.93
CENPV	5E-05	0.73	0.73	0.73	IL11	1E-04	0.98	0.98	1
BCR	5E-05	1	1	1	SUB1	1E-04	0.99	0.99	1
CD19	5E-05	0.31	1	1	IL3	1E-04	1	1	1
CD34	5E-05	1	1	1	POLD4	1E-04	0	0.73	0.99
MECOM	6E-05	1	1	1	POLE4	1E-04	0	0.73	0.99
CSF3	6E-05	1	1	1	CSF2	1E-04	1	1	1
CNTF	7E-05	1	1	1	RARA	1E-04	1	1	1
ZBTB16	7E-05	1	1	1	JAK2	1E-04	0.95	0.95	0.98
MEIS1	7E-05	1	1	1	CD22	1E-04	0	0.97	1
HOXA9	7E-05	0.99	0.99	1	RUNX1T1	1E-04	0.99	1	1
ANPEP	7E-05	1	1	1	BMI1	1E-04	0.96	0.99	1

Azacitidine is recommended as a front-line treatment for older patients with AML who are not candidates for intensive treatment regimens [141, 142].

Clofarabine is a medication used to treat acute lymphoblastic leukemia (ALL) in children and young adults aged 1 to 21 years who have already had at least two other types of treatment. It is usually given after other treatments have failed. Clofarabine is a second-generation purine analog that displays potent inhibition of DNA synthesis and has a favorable pharmacologic profile [143, 144].

Aclarubicin is a medication used to treat acute non-lymphocytic leukemia, a cancer of the blood and bone marrow [5]. It has been used as induction treatment in patients with acute myeloid leukemia (AML) who were either refractory to initial induction chemotherapy or in relapse [2, 145].

Dasatinib is a medication used to treat certain types of leukemia, including chronic myeloid leukemia (CML) and Philadelphia chromosome-positive acute lymphoblastic leukemia (ALL). It is approved for use as a first treatment for CML and in adults who can no longer benefit from other leukemia medications, including imatinib (Gleevec), or in those who cannot take these medications because of side effects. Dasatinib is a second-generation BCR-ABL1 kinase inhibitor [146-148].

Tetradecanoylphorbol Acetate (TPA) is a potent tumor promoter often employed in biomedical research to activate the signal transduction enzyme protein kinase C (PKC)[2]. TPA is also a potent inducer of differentiation in human

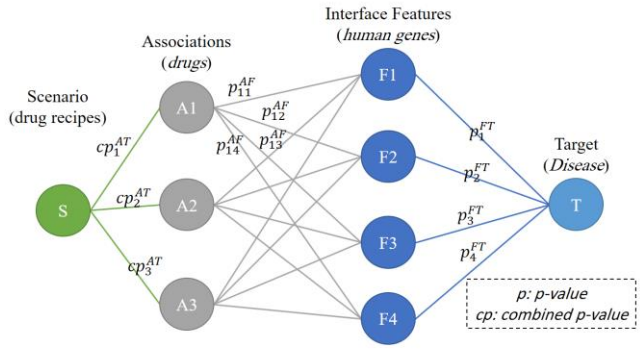
promyelocytic leukemia cells[1]. TPA has been successfully administered to patients with myelocytic leukemia and has produced therapeutic effects that led to temporary remission[1]. Additional studies with TPA after the determination of optimum dosing regimens are needed to determine whether long-lasting or permanent remissions of myelocytic leukemia can be achieved [149-151].

Venetoclax is a drug that is approved to treat acute myeloid leukemia (AML) that is newly diagnosed. It is used in adults aged 75 years and older or adults who cannot be treated with intensive induction chemotherapy. It is given with either azacitidine, decitabine, or low-dose cytarabine. Venetoclax has also shown promise for treating AML, which has elevated levels of Bcl-2 [72, 105, 152].

1.2.1. Objectives

Despite the existence of various studies on useful drugs for leukemia, the reasons shown in Figure 1 have led to lack of comprehensive statistical research on the subject. The use of artificial intelligence, on the other hand, has been considered in various medical applications in recent years, from protein folding [153], medical imaging [154, 155], cohort studies [156], until core fundamental changes in neural networks [157].

The goal of this research is suggesting drug combinations to manage/treat Leukemia using the RAIN protocol, which employs artificial intelligence to recommend drug combinations for managing or treating diseases [158]. The RAIN protocol has been used in recent years to propose medicinal compounds for diseases such as cancers [154, 159-161].



(a) (b)

Figure 3

The general structure of the GNN model to suggest an effective drug combination in the management of disease using human proteins/genes as interface features.

2. Method

The RAIN protocol has three stages. The first stage uses artificial intelligence to suggest a drug combination for managing/treating a disease. In the second stage, a systematic review of recent articles and clinical trials is conducted using Natural Language Processing to evaluate the effectiveness of different permutations of the combination.

The number of articles in each step of STROBE checklist are shown in Figure 2. In the third stage, Network meta-analysis is used to evaluate the effectiveness of drugs and related human proteins/genes.

2.1. Stage I: Graph Neural Network

The GNN in the RAIN protocol is a method that proposes cooperations between associations for a target. It takes as input associations with known p-values from a network meta-analysis and outputs cooperations with small significance.

The proposed model has forward and backward steps. In the forward step, the GNN algorithm computes combined p-values between associations and the target, selecting the association with the smallest combined p-value. In the backward step, p-values between interface features and the target are updated based on selected associations. The significance of cooperating associations is computed by multiplying their combined p-values. These steps are repeated until significance is below a threshold. The process is shown in Figure 3.

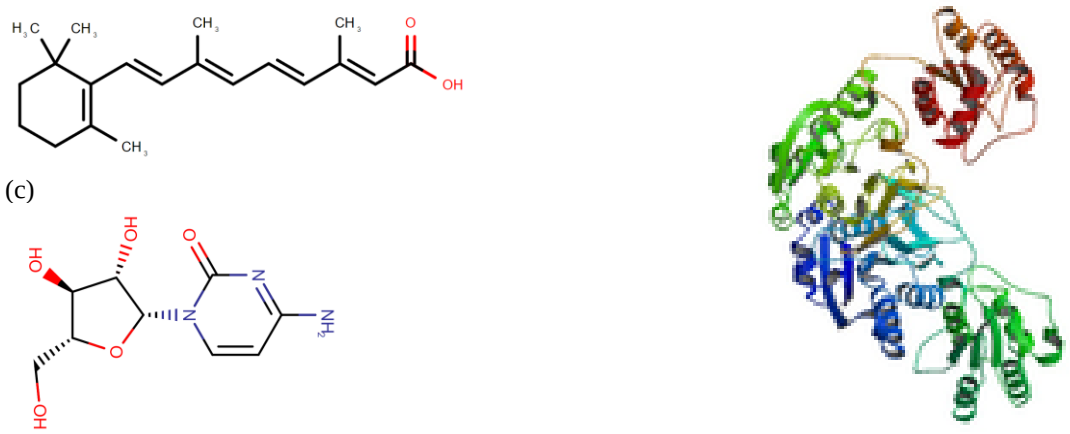


Figure 4

Drug structure for (a) Tretinoin, (b) Asparaginase, (c) Cytarabine from https://www.drugbank.com/

2.2. *Stage II: A comprehensive Systematic Review*

In this stage a process for validating the findings of a GNN model through a systematic evaluation of recommended medications is described. A systematic review is conducted using databases such as Science Direct, Embase, Scopus, PubMed, and Web of Science, as well as Google Scholar, to access previously published articles for review.

We have used of a semantic search technique based on Natural Language Processing (NLP) instead of a manual search within databases. This technique searches MeSH for every single term and can find a broader and more accurate range of articles in a relatively short period of time.

2.2.1. *Information sources*

We have used of an NLP-based systematic review to identify relevant studies within various databases, including Science Direct, Embase, Scopus, PubMed, and Web of Science, as well as Google Scholar. The goal is to validate the suggested drug combination from an in-house GNN model by analyzing data from a large-scale clinical trial. Keywords are extracted from the outputs of the GNN model and the Leukemia subscription.

2.2.2. *Search strategy*

A natural language processing technique is used to conduct a semantic search of publication titles and abstracts within various databases. This technique allows for the consideration of MeSH phrases as potential search keywords due to the value of semantic search.

2.2.3. *Study selection*

At the beginning of the process, duplicate research is removed. A list of all remaining research titles is compiled during the evaluation phase to filter the research in a structured manner. In the first phase of the systematic review, screening, the titles and abstracts of the remaining research are thoroughly reviewed and some studies are excluded based on selection criteria.

In the second step, the competency evaluation, the full text of the remaining research from the screening phase is thoroughly reviewed based on selection criteria, and several unrelated studies are eliminated. To prevent personal bias from influencing resource selection, an expert and an NLP Question-Answering (QA) agent conduct independent research and data extraction. The expert must provide a detailed explanation for why a study was not selected. The QA agent assigns a score to each article based on the questions posed, and articles with the lowest scores are removed. Questions include, "Is this drug effective for the treatment of leukemia?" with "this drug" being replaced by different drugs for each output of the intelligent system. If there is disagreement between the expert and the QA agent's output, the expert will review the contentious research.

2.2.4. *Quality evaluation*

A checklist is used to evaluate the quality of the remaining publications based on the specific type of research

being conducted. The STROBE method is often used to evaluate the quality of observational studies. The checklist is divided into six broad sections: title, abstract, introduction, methodology, results, and discussion, with a total of 32 fields including subscales.

Each of the 32 fields in the checklist represents a distinct aspect of a study's methodology, including title, problem statement, study objectives, study type, statistical population, sampling method, sample size, variable and procedure definitions, data collection methods, statistical analysis techniques, and results. A score of 32 is considered the maximum that can be achieved during the quality assessment phase using the STROBE checklist. Articles with a score of 16 or higher are considered to be of moderate or high quality.

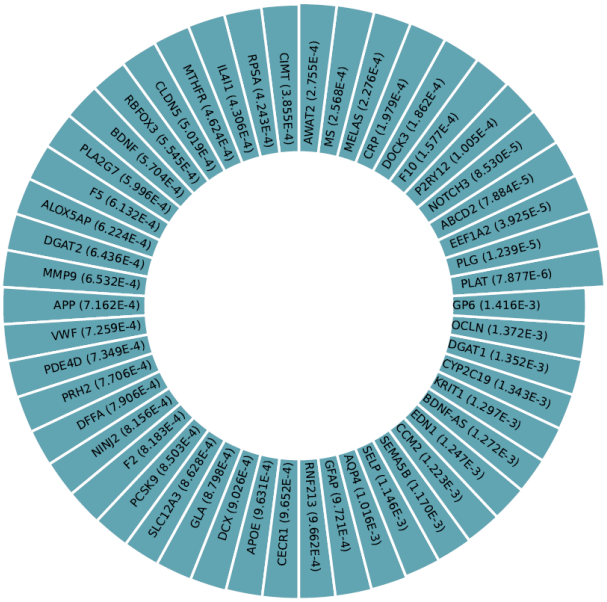


Figure 5

p-values between affected human proteins/genes and Leukemia

Table 3

properties of proposed drugs as effective drugs to Leukemia management.

Drug Name	Accession Number	Type		Formula	Mechanism of Action
		Small Molecule	Biotech		
Tretinoin	DB00755	*		$C_{20}H_{28}O_2$	Tretinoin attaches to three types of retinoic acid receptors, known as alpha, beta, and gamma. The first two types have been linked to specific cancers, while the third type is related to the impact of retinoids on skin and bone tissues.
Asparaginase	DB00023		*	$C_{1377}H_{2208}N_{382}O_{442}S_{17}$	Asparagine is a non-essential amino acid that helps with cell growth and DNA, RNA, and protein synthesis. Lymphoblastic leukemic cells can't

				produce asparagine on their own and rely on external sources. L-asparagine from E. coli can deplete plasma levels of asparagine in leukemic cells, leading to reduced cell growth and the activation of cell-death mechanisms. Normal cells can synthesize asparagine and are less affected by treatment with the enzyme asparaginase.
Cytarabine	DB00987	*	$C_9H_{13}N_3O_5$	Cytarabine is a drug that damages DNA and incorporates into it. It is toxic to many proliferating cells and is most effective against cells undergoing DNA synthesis. It works by inhibiting DNA polymerase and can also incorporate into both DNA and RNA.

Figure 6

p-values between affected human proteins/genes and Leukemia after implementing Scenario 4.

2.3. Stage III: Network meta-analysis

The third stage involves using a network meta-analysis to examine the effects of proposed synthetic drug combinations on human proteins/genes, which leads a network meta-analysis is used to assess multiple drugs in a single study. This method combines direct and indirect data between disease and drugs, using proteins/genes as an interface feature within a network of randomized controlled trials. It helps to measure the comparative efficacy of commonly used drugs in clinical practice. The efficacy of each drug is evaluated based on input biological data.

3. Results

3.1. Stage I: Graph Neural network

The GNN recommended drug combination is Tretinoin, Asparaginase, and Cytarabine. Table 1 shows the p-value of combining these drugs.

Table 4

some important research studies for proposed drugs in Leukemia managements

Authors	Tretinoin	Asparaginase	Cytarabine
[162]		*	*
[163]		*	*
[164]		*	*
[165]	*		*
[166]	*		*
[167]	*		*
[168]	*		*
[169]	*		*
[170]	*		*
[171]		*	*
[172]		*	*
[173]	*		*
[174]	*		*
[175]	*		*
[176]	*		*
[177]		*	*

[178]		*	*
[179]		*	*
[180]		*	*
[181]	*		*
[182]		*	*
[183]		*	*
[184]		*	*
[185]	*		*
[96]	*		*
[186]	*		*
[187]		*	*
[188]		*	*
[189]		*	*
[190]	*		*
[191]	*		*
[192]	*	*	
[193]	*	*	
[194]	*	*	
[195]	*	*	

For example, the p-value between Leukemia and Tretinoin (Scenario 1) is 0.01 and decreases to 0.000088 when Asparaginase is added (Scenario 2). The p-value after applying the third scenario (3E-5) indicates that the proposed drug combination had a good effect in managing the disease.

Table 2 shows how the p-values between human proteins/genes and Leukemia change with new scenarios. The 'S0' column shows the p-value between Leukemia and the corresponding affected human proteins/genes. The 'S1' column shows the combined p-value when Tretinoin is used. In the 'S3' column, many of the p-values between Leukemia and human proteins/genes reach 1, indicating a weakening of the importance of the target proteins/genes.

3.2. Stage II: A comprehensive Systematic Review

This stage examines the effect of the mentioned medications on the treatment of leukemia. Articles with this focus were collected and systematically evaluated until July 2022 according to PRISMA principles and the RAIN framework. 251 potentially relevant articles were found and imported into the EndNote reference management system. 178 of these were duplicates and were disregarded. After reviewing the titles and abstracts of the remaining 131 papers and considering the inclusion and exclusion criteria, 40 studies were eliminated during the screening phase. During the eligibility evaluation, there were 120 studies remaining, and 47 were eliminated after their full texts were reviewed and the inclusion and exclusion criteria were considered. In the quality evaluation stage, 15 of the remaining 16 studies were eliminated based on their STROBE checklist scores and poor methodological quality, leaving 35 cross-sectional studies for the final analysis.

The full texts of the articles were analyzed and each paper was scored using the STROBE checklist, as shown in Figure 3. Details and characteristics of these articles are provided inFigure 5

p-values between affected human proteins/genes and Leukemia

Table 3. The structures of the drugs are shown in **Error! Reference source not found.**. Table 4 displays the properties of the drugs.

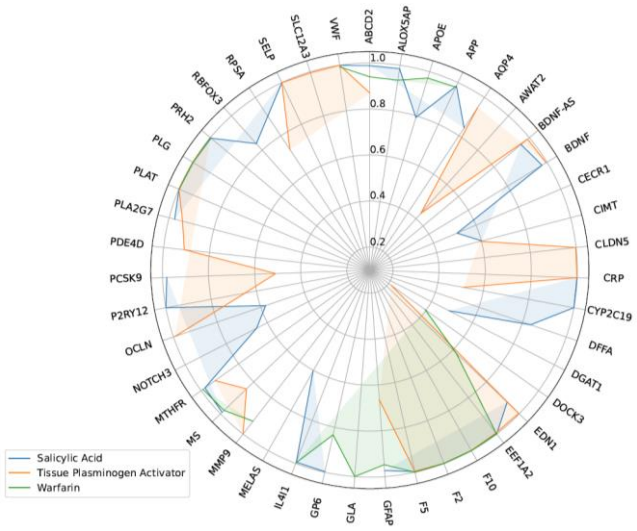


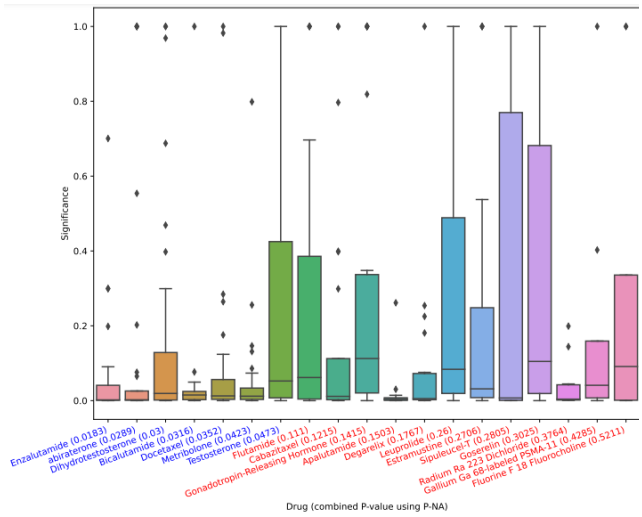
Figure 7

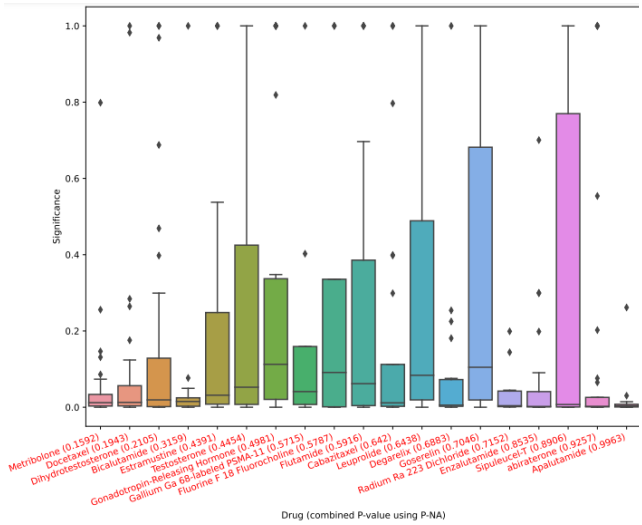
radar chart for p-values between Leukemia and affected proteins/genes, after consumption of each drug.

3.3. Stage III: Network Meta-Analysis

Figure 5 displays the p-values between human proteins/genes affected by Leukemia, while **Error! Reference source not found.** shows the p-values after

applying the third scenario. **Error! Reference source not found.** uses a radar chart to show the effectiveness of drugs chosen by the drug selection algorithm, by displaying the p-values between Leukemia and human proteins/genes after taking the selected drugs. Figure 8 presents the p-values between associations and targets using various interface features. P-values less than .01 and .05 are indicated in green and blue, respectively. Each colored line represents the effectiveness of the corresponding drug in that scenario.





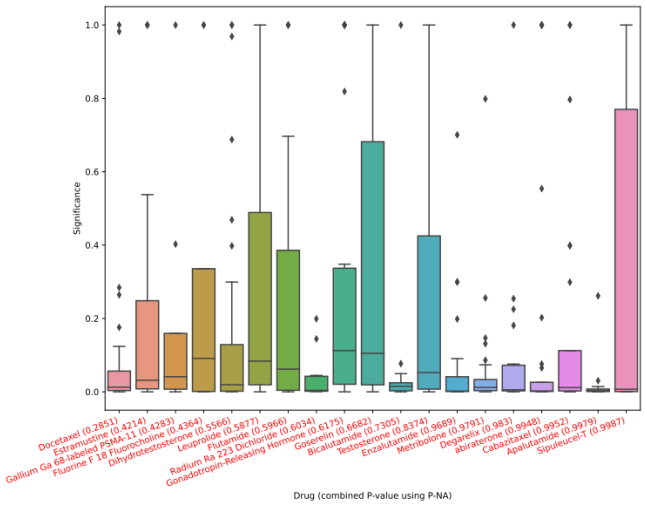


Figure 8
p-values between associations and target, using different interface features. (a) Overall, (b) after first drug from (a) is used, (c) after first drugs of (a) and (b) are used.

4. Discussion

Information on prescription drugs is used to research drug interactions, food combinations, side effects, and concerns about serious conditions. Several reliable websites, including Medscape, WebMD, Drugs, and Drugbank, were used to compare medications side-by-side. These online databases examined drug pairs and revealed that some interactions can occur between certain medication combinations. However, at this time, none of these websites find any significant interactions between Tretinoin, Asparaginase, and Cytarabine.

5. Conclusion

Leukemia is a type of cancer that affects the body's blood-forming tissues, including the bone marrow and the lymphatic system. It usually involves the white blood cells, which are potent infection fighters that normally grow and divide in an orderly way as the body needs them. Using a combination of drugs can improve the treatment of leukemia. A common chemotherapy treatment for acute leukemias begins with induction chemotherapy, followed by intensification or consolidation chemotherapy. Under RAIN protocol, our Graph Neural Network suggested combining Tretinoin, Asparaginase, and Cytarabine to target human genes/proteins associated with leukemia. The results show a significant improvement in leukemia treatment.

Authors' Contributions

All authors equally contributed to this study.

Declaration

In order to correct and improve the academic writing of our paper, we have used the language model ChatGPT.

Transparency Statement

Data are available for research purposes upon reasonable request to the corresponding author.

Acknowledgments

We would like to express our gratitude to all individuals helped us to do the project.

Declaration of Interest

The authors report no conflict of interest.

Funding

According to the authors, this article has no financial support.

Ethical Considerations

Not applicable.

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