REVIEW
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Selenium as a complementary therapeutic agent in leukemia: A systematic review of preclinical and clinical evidence

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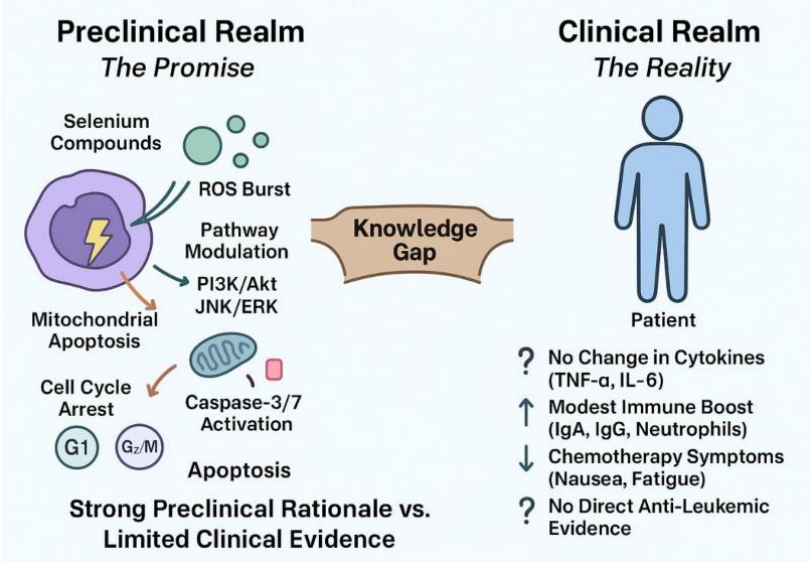
Abstract

Background: Selenium deficiency is associated with impaired immunity and leukemogenesis. Selenium compounds exhibit antiproliferative and proapoptotic effects in leukemic models, indicating therapeutic potential. However, no comprehensive review has assessed selenium's impact on leukemia patients. This systematic review addresses that gap and highlights areas for future research. **Methods:** Following PRISMA guidelines, literature was reviewed from Medline, CINAHL, Scopus, ScienceDirect, and EBSCO in May 2025. A detailed search strategy used Medical Subject Headings terms and keywords including "selenium," "leukemia," "apoptosis," and "seleno-proteins." We employed the Population, Intervention, Comparison and Outcome framework. **Results:** Of 339 records identified, 21 studies met inclusion criteria, spanning preclinical and clinical evidence. Preclinical studies consistently show selenium induces apoptosis, activates caspase pathways, and modulates cell signaling. Clinical studies suggest selenium is safe and may enhance immune markers and liver function, though effects on inflammatory cytokines vary. **Conclusion:** To our knowledge, this is the first comprehensive review on this topic for leukemia. Selenium shows strong anticancer properties, and holds promise as an adjunctive treatment for leukemia. While its direct therapeutic role remains under investigation, this review identifies key research gaps and calls for rigorous clinical trials to guide future practice.

Keywords: selenium; complementary; systematic review; leukemia; apoptosis; leukemogenesis; preclinical evidence; clinical evidence



Author contributions

Conceptualization: Alqaisi O; Methodology: Alqaisi O, Al-Ghabeesh S; Software: Alqaisi O; Formal analysis: Alqaisi O; Investigation: Alqaisi O, Al-Ghabeesh S; Resources: Alqaisi O; Data curation: Alqaisi O; Writing – original draft: Alqaisi O; Writing – review & editing: Alqaisi O, Subih M. Alqaisi O and Subih M performed the systematic literature search and study selection. Alqaisi O and Subih M drafted the initial manuscript. Alqaisi O and Subih M provided critical revisions and input to improve the content and clarity of the manuscript. Tai P, Joseph K, Qirim W, Sijarina L, Dibas M and Al-Ghabeesh S contributed to data interpretation, manuscript editing, and provided feedback on the manuscript. All authors have read and approved the final manuscript.

Competing interests

The authors declare no conflicts of interest.

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Abbreviations

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; HSCT, hematopoietic stem cell transplantation; MAPK/ERK, mitogen-activated protein kinase/extracellular signal-regulated kinase; PI3K/Akt, phosphatidylinositol 3-kinase/protein kinase B; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT, randomized clinical trial; ROS, reactive oxygen species; Se, selenium; SeNPs, selenium nanoparticles; MRD, minimal residual disease.

Citation

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Introduction

Leukemia is a type of cancer that arises from the transformation of hematopoietic cells in the bone marrow into malignant cells [1]. Leukemia is broadly categorized into lymphoid and myeloid types, depending on whether it affects lymphocytes or myeloid cells. In 2021, a global cancer trend observatory reported a worldwide incidence of 474,519 cases, including 67,784 in North America. The Age-Standardized Rate is approximately 11 per 100,000, and the mortality rate is around 3.2 per 1,000 [2, 3]. A notable concern is the increased burden of hematologic malignancies linked to late referrals for palliative care.

Selenium (Se) is a vital trace element and an essential micronutrient involved in various biological processes. Its daily intake varies based on geographical and dietary factors; in the United States, adults typically consume 100–125 µg/day, although levels can drop to 60–90 µg/day in some regions such as the Eastern Coastal Plain and the Northwestern part of China [4].

Selenium functions as a potent antioxidant and immune system enhancer [5, 6]. It is critical for the biosynthesis of several seleno-proteins [7, 8]. These enzymes play essential roles in mitigating oxidative stress and regulating inflammation. Selenium is also concentrated in tissues associated with hematopoiesis and immune function, including the liver, spleen, bone marrow, and lymph nodes [9]. Selenium deficiency in both humans and animal models has been linked to impaired antioxidant defense, reduced immunoglobulin production, and dysfunctional detoxification pathways [10].

In the context of hematologic cancers such as leukemia, selenium has emerged as a potential complementary treatment, particularly in palliative care settings [9]. Leukemic patients often exhibit low serum selenium levels [11], and selenium supplementation has shown promise in modifying disease parameters. For instance, selenium-cystine (diselenodialanine) has been reported to reduce total and immature leukocyte counts in patients with chronic myeloid leukemia (CML) and acute myelogenous leukemia (AML) [12].

Mechanistically, selenium's antileukemic effects are thought to involve its antioxidant and anti-inflammatory properties, suppression of malignant cell proliferation, and promotion of apoptosis via activation of specific signaling pathways [13]. Moreover, selenium compounds like methyl-seleninic acid have demonstrated chemosensitizing effects in B-cell lymphomas, possibly by inhibiting nuclear factor-κB (NF-κB) and generating active selenium species [14]. Despite these promising results, current clinical evidence is limited and fragmented, underlining the need for further investigation into selenium's therapeutic potential in hematologic malignancies.

This study aims to answer the review questions: (1) What is the therapeutic potential of selenium in the treatment of leukemia on the basis of preclinical evidence? (2) What are the current gaps in clinical research that limit its clinical application?

Materials and methods

Study design and registration

This systematic review was designed and conducted in full compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines. The protocol was prospectively registered in the PROSPERO international database (CRD420251065124) prior to data extraction and analysis. The review sought to comprehensively identify, evaluate, and summarize available preclinical and clinical evidence regarding the therapeutic potential of Se and its compounds in the treatment and management of leukemia. All methodological steps, including database search, eligibility assessment, data extraction, and quality appraisal, were performed systematically to ensure rigor, reproducibility, and transparency in reporting.

Eligibility criteria

The inclusion and exclusion criteria were established a priori and are summarized in Table 1. In general, studies were eligible for inclusion if they met the following criteria: (1) Preclinical studies: *In vitro* experiments using human or animal leukemia cell lines (e.g., HL-60, NB4, K562) or *in vivo* studies employing animal models of leukemia (e.g., murine models of AML, acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL), or CML) that investigated selenium or selenium-based compounds as therapeutic or adjunctive interventions. (2) Randomized controlled trials (RCTs): Clinical studies involving human participants with leukemia or other hematologic malignancies that examined selenium supplementation as a treatment or co-therapy and reported patient-relevant biochemical or clinical outcomes. No restrictions were applied regarding publication date, country of origin, or study setting to ensure comprehensive search. Only English-language peer-reviewed publications were included. Eligibility was determined using the Population, Intervention, Comparison, and Outcome (PICO) framework. "Population" includes different stages of disease, healthcare settings and geographical location. "Intervention" includes dose, frequency, mode of delivery (oral or intravenous) and duration. "Comparison" of options includes standard care, placebo, different intervention or other controls. "Outcome" includes short or long-term survival and tests for measuring response.

Data sources and search strategy

A comprehensive and systematic literature search was conducted across five major electronic databases: PubMed/Medline, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Scopus, ScienceDirect, and Elton B. Stephens Company online database-hosting platform used by libraries (EBSCOhost). The search covered studies published between January 2000 and May 2025, ensuring the inclusion of both classical and recent experimental and clinical evidence. The strategy combined Medical Subject Headings (MeSH) with free-text keywords, applying Boolean operators "AND" and "OR" to optimize sensitivity and specificity. The primary search string included combinations such as: ("selenium" OR "selenite" OR "seleno-methionine" OR "methyl-seleninic acid") AND ("leukemia" OR "acute myeloid leukemia" OR "acute lymphoblastic leukemia" OR "hematologic malignancy") AND ("apoptosis" OR "oxidative stress" OR "chemotherapy" OR "immune modulation"). Where applicable, filters were applied to limit the results to English-language, peer-reviewed, and original research articles. The complete list of search terms and Boolean operator combinations used across databases is shown in Table 2.

Two independent reviewers (OA and MS) performed the searches. Following the initial broad search, a second, targeted search was conducted to retrieve additional preclinical studies due to the limited number of clinical trials identified in the first round. All retrieved citations were exported to EndNote X9 for reference management and duplicate removal prior to screening.

Study selection

Study selection was performed in accordance with the PRISMA 2020 guidelines. Titles and abstracts were screened independently by two reviewers, and the full text of each potentially eligible article was obtained for detailed evaluation. Any disagreements were resolved through discussion, and when necessary, a third investigator was consulted. Preclinical studies encompassed both *in vitro* leukemia cell-line experiments and *in vivo* animal models. Clinical studies included all major leukemia types—AML, ALL, CLL, and CML—regardless of patient age, sex, or treatment stage. Eligible studies were required to assess selenium's impact on at least one of the following: treatment efficacy, oxidative stress modulation, apoptosis, redox signaling, or interaction with chemotherapeutic regimens. The overall study identification and selection process (including the number of records identified, screened, excluded, and finally included) followed the PRISMA 2020 guidelines. The diagram summarizes how studies progressed through each stage of the review process, from initial database search to final inclusion.

Quality assessment of included studies

Quality and risk-of-bias assessments were performed according to the respective study design. For randomized controlled trials, the Joanna Briggs Institute (JBI) Critical Appraisal Checklist was used to evaluate randomization, allocation concealment, blinding, completeness of outcome data, and statistical analysis. For preclinical animal and *in vitro* studies, quality was assessed using a combination of the ARRIVE Essential 10 guidelines and the SYRCLE Risk of Bias Tool. These frameworks address experimental design, animal welfare, randomization, blinding, sample size justification, and data reporting transparency. Each study was independently evaluated by two reviewers, and discrepancies were resolved through consensus. Studies meeting over 70% of appraisal criteria were categorized as low risk of bias, while those below that threshold were considered moderate or unclear risk. The detailed outcomes of the quality assessments are summarized in Supplementary Table S1 [10, 15, 16] and Supplementary Table S2 [17–32], which outline individual study ratings, total scores, and overall appraisals. Supplementary Table S1 shows that using the 13 questions of the JBI checklist, the 3 randomized studies scored 91%, 100% and 100%, indicating reasonable methodological quality.

Synthesis of results

The database search yielded a total of 219 + 120 = 339 records. After removing 60 duplicates, 279 unique studies were screened based on titles and abstracts. Of these, 109 full-text articles were retrieved for detailed eligibility assessment. Figure 1 showed the 21 studies included in the final qualitative synthesis of three RCTs, one clinical phase I study and 17 preclinical studies.

Table 1 Summary of the inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Population/Subject: 1. Preclinical studies: *In vitro* studies using leukemia cell lines (e.g., HL-60, NB4, K562) or *in vivo* studies using animal models of leukemia (e.g., murine models of AML, ALL, CLL, or CML). 2. Clinical studies: patients diagnosed with hematological malignancies including leukemia, lymphoma, and pediatric cancer patients, including all ages, sex, and disease stages. Intervention: 1. Studies evaluating selenium or its compounds (e.g., sodium selenite, selenomethionine, methylseleninic acid, selenodiglutathione, SeNPs) as a therapeutic agent, either alone or in combination with standard leukemia treatments (e.g., chemotherapy, targeted therapies). 2. Studies examining selenium effects on leukemia cell proliferation, apoptosis, cell cycle arrest, oxidative stress, or LSC targeting. Study Design: 1. Preclinical: Experimental studies (*in vitro* or *in vivo*) and case reports with clear methodology, including selenium treatment. 2. Clinical: Randomized controlled trials, addressing selenium's therapeutic role or serum levels in leukemia patients.	1. Studies on where selenium is used as a diagnostic marker or biomarker without therapeutic implications. 2. Systematic reviews or meta-analyses or non-experimental studies for preclinical research (e.g., narrative reviews, editorials, or opinion pieces without primary data)
Outcomes: 1. Outcomes related to selenium effects on leukemia cells or animal models, such as: apoptosis, cell cycle arrest, or DNA damage. 2. Effects on leukemia stem cells (e.g., via oxidative stress or eicosanoid pathways). 3. Modulation of selenoproteins (e.g., GPX1, GPX4) or signaling pathways (e.g., JNK1, p21, p27, PML/RARα), and selectivity for leukemia cells over healthy cells.	–
Publication Type and Language: 1. Peer-reviewed journal articles, conference proceedings, or published theses. 2. Studies published in English. 3. No restriction on publication date to capture the full scope of preclinical and clinical research.	–

AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; LSC, leukemia stem cell; SeNPs, selenium nanoparticles.

Table 2 List of keywords or Boolean operators used in research across five databases

No.	Keywords or Boolean operators
1	Selenium/OR Selenocysteine/OR Selenomethionine OR (Se adj1 (salt or supplementation)) OR Selenite OR Selenocystine/OR Selenomethionine
2	Neoplasms/OR neoplasm OR cancer OR tumor OR malignant OR hematologic cancer OR Leukemia OR lymphoma
3	1 AND 2
4	limit to English
5	therapeutic/OR preclinical/OR clinical/OR apoptosis/OR leukemia stem cell
6	4 AND humans/OR 4 AND animals/cell line
7	3 AND 5

Se, selenium; adj1, Adjuvant 1 (means enhancer or helper).

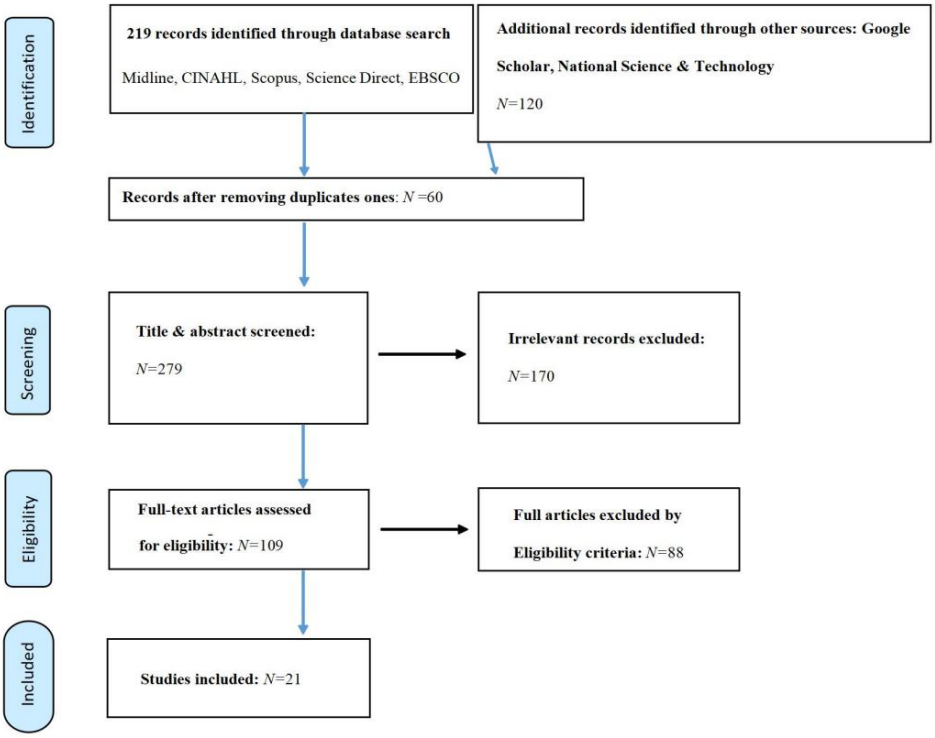

Figure 1 PRISMA flow diagram of the systematic search strategy.
PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Results

Preclinical studies investigated the molecular mechanisms and therapeutic potential of selenium and its derivatives using leukemia cell lines or animal models. The RCTs evaluated selenium supplementation as an adjunct to standard therapies (chemotherapy or hematopoietic stem cell transplantation (HSCT)) in leukemia and lymphoma (LL) patients.

Preclinical studies

Seventeen preclinical studies were included, comprising both *in vitro* experiments using leukemia cell lines (e.g., HL-60, NB4, K562, U937) and *in vivo* animal models (murine leukemia or xenograft models). The key design characteristics and outcomes of these studies are summarized in Supplementary Table S2. Across preclinical data, selenium compounds, particularly sodium selenite, methyl-seleninic acid, and selenium nanoparticles, induced apoptosis, oxidative stress, DNA fragmentation, and differentiation in leukemia cells, while sparing healthy cells in most cases. In animal models, selenium administration reduced tumor growth and enhanced the effects of chemotherapeutic drugs.

Induction of apoptosis. All preclinical experiments demonstrated that selenium promotes apoptosis in leukemia cell types. The mechanisms involved the activation of caspase-3/7, the collapse of the mitochondrial membrane potential, and the breakage of nuclear DNA. Han et al. reported that ERK facilitates caspase-dependent apoptosis in NB4 cells [17]. Sewell et al. reported increased caspase-3 expression in HL-60 and THP-1 cells ($P < 0.05$), indicating the triggering of apoptosis [7].

Oxidative stress and the generation of reactive oxygen species (ROS). Seven studies reported selenium-induced ROS generation as a key cytotoxic mechanism. Last et al. reported that seleno-diglutathione (SDG)-induced apoptosis in lymphoma cells was reversed by N-acetylcysteine (NAC) ($P < 0.01$) [18]. Wang et al. demonstrated that selenium-mediated differentiation in AML cells was abolished by NAC, confirming its redox dependence [27]. Fang et al. reported similar findings in t(8;21) AML cells via the use of selenium nanocarriers [25].

Cell cycle arrest and differentiation. Selenium exposure induced cell cycle arrest was documented in three studies. Shi et al. reported G2/M arrest in HL-60 cells (a human promyelocytic leukemia cell line) [19], whereas Wu et al. and Shi et al. confirmed G1 arrest in the Jurkat and HL-60 lines [19, 24]. Additionally, Fang et al. and Wang et al. demonstrated that selenium promoted differentiation in AML cell lines [25, 27], linked to ROS signaling pathways.

Modulation of cancer cell proliferation signals. The mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) and phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt) signaling pathways are commonly affected, indicating their involvement in the cellular response to treatment. Han et al demonstrated that ERK activation is essential for selenium-induced apoptosis [17]. Wu et al. reported that selenium induced apoptosis via PI3K/Akt inhibition ($P < 0.01$) [24]. Shi et al. supported these findings through transcriptomic analyses, highlighting caspase-3 upregulation and Bcl-2 downregulation ($P < 0.05$) [19].

Synergistic effects of antitumor drugs *in vivo*. Shi et al. and An et al. validated the efficacy of selenium in leukemia-bearing mice, resulting in reduced tumor burden and increased apoptosis ($P < 0.05$) [19, 31]. Wang et al highlighted the synergistic effects of selenium with arsenic trioxide in acute promyelocytic leukemia (APL) cells, enhancing PML-RARα degradation [27]. Spengler et al. reported that selenium compounds synergize with vincristine but antagonize cisplatin, suggesting context-specific drug interactions [28].

Cyto-protection in healthy cells. Sonaa et al. reported that selenium and genistein reduce DNA damage and apoptosis in healthy lymphocytes exposed to cisplatin/mitomycin C, suggesting the potential role of selenium in minimizing chemotherapy-induced toxicity in normal cells [32].

Using nanotechnology in the treatment. Selenium nanoparticles (SeNPs) have emerged as a promising candidate, demonstrating efficacy in inducing cytotoxicity in cancer cells [33]. It holds the potential to overcome pharmaceutical resistance and mitigate the toxicity associated with conventional chemotherapy agents. SeNPs serve as excellent carriers for delivering chemotherapy agents

precisely to their intended locations. It exhibits selective efficacy against malignant cells while sparing normal cells, enhancing bioavailability. The dual prooxidant and antioxidant effects of SeNPs offer diverse avenues for exploration across a spectrum of clinical conditions [33].

Shared outcomes across preclinical studies. Preclinical studies have consistently shown that selenium induces apoptosis via caspase activation and mitochondrial disruption, with ROS playing a key role in redox-dependent cell death and differentiation. Selenium also causes cell cycle arrest (G1/G2-M) and modulates the MAPK/ERK and PI3K/Akt pathways [7, 29–34]. Animal models have confirmed its tumor-reducing effects and synergy with treatments such as arsenic trioxide and vincristine. All clinical and preclinical studies are summarized in the tables [7, 34]. Risk of bias assessment using the SYRCLE tool showed variable quality across animal studies, with most studies lacking adequate randomization and blinding procedures.

Clinical studies

The three RCTs assessed various forms of selenium supplementation, such as sodium selenite, seleno-methionine, and selenium glycinate in patients undergoing chemotherapy or HSCT for hematologic malignancies (Supplementary Table S3) [10, 15, 16]. The outcomes included: Inflammatory cytokines, such as tumor necrosis factor and interleukins (e.g., TNF-α, IL-1β, IL-6), immune markers (neutrophil counts, immunoglobulin levels), clinical symptoms (fatigue, nausea, vomiting) and organ function (renal, liver).

Across all studies, selenium was well tolerated with no significant adverse effects reported. While the clinical impact varied, several studies showed positive trends in immune function and reduced toxicity during treatment.

Immunological effects. Two clinical trials revealed increases in immunological markers after selenium treatment. Rocha et al. reported increased neutrophil, IgA, and IgG levels after selenium treatment in pediatric patients with solid tumor [10]. Vieira et al. reported modest immune benefits in patients with juvenile leukemia [16]. These findings suggest that immune-stimulatory effects of selenium may be more pronounced in non-leukemic pediatric populations. Daeian et al. assessed the impact of selenium on inflammatory cytokines in adult patients after HSCT [15]. No statistically significant differences were noted in TNF-α ($P = 0.13$), IL-1β ($P = 0.88$), or IL-6 ($P = 0.96$) levels on day +7 between the selenium and placebo cohorts. Despite a considerable increase in IL-6 from baseline to day +7 ($P < 0.001$) in both groups, the levels decreased by day +14 ($P < 0.001$), suggesting that selenium did not significantly affect cytokine dynamics during HSCT [15].

Liver function and hematologic effects. Improved liver enzyme profiles were noted by Vieira et al. [16], with elevated alanine aminotransferase (ALT) levels reduced from 52.6% to 26.3% post selenium treatment. However, Rocha et al. [10] reported no significant hematologic alterations in leukemic individuals, suggesting selenium may have limited effects on core hematologic parameters.

Patient tolerance, pharmaco-kinetcs/dynamics and dose. Selenium supplementation was associated with improved chemotherapy tolerance. Vieira et al. [16] reported reductions in nausea, fatigue, and appetite loss, with benefits sustained over one year. These findings support potential role of selenium in alleviating gastrointestinal and systemic side effects of cancer therapy. All clinical trials concluded that selenium was well tolerated, with no serious adverse events reported. Evans et al. conducted a pharmaco-dynamic study (phase I design without placebo control) in which adult patients received 400 µg/day of selenium compounds for eight weeks and reported no significant side effects [34]. Similar tolerability was noted in pediatric studies [10]. These data confirm the advantageous safety profile of selenium within the assessed dose range. In summary, there is no single standard selenium dose for leukemia and published studies used 100–400 ug/day for oral selenium (mostly selenomethionine or selenized yeast) and 1–10 mg/day for intravenous sodium selenite in oncology settings of small trials and pilot studies. These studies were performed on selenium-adequate populations [35].

Organic versus inorganic selenium forms. Selenium shows complex pharmacokinetics influenced by its chemical form, with differences in absorption, distribution, metabolism, and excretion between inorganic (e.g., selenite) and organic forms (e.g., selenomethionine) [36]. Organic forms are generally absorbed more efficiently in the small intestine and incorporated into body proteins to become a slow-release selenium pool; while inorganic forms are more rapidly metabolized and excreted. Inorganic selenium is used for selenoprotein synthesis, such as glutathione peroxidase and selenoprotein P. Human serum albumin-bound selenium is composed of inorganic selenium [37].

Discussion

This systematic review highlights selenium's multifaceted potential as a supportive or therapeutic agent in leukemia treatment, combining evidence from clinical and preclinical studies. Some included clinical studies [10, 16] involved mixed pediatric cancer populations, including solid tumors alongside leukemia patients, which may limit the specificity of findings to leukemia populations. Mixed cancer cohorts limit drawing conclusions specific to leukemia or its subtypes. Evans (2020) was not an RCT but represents a single-arm phase I pharmacodynamics study without a placebo control [34]. In addition, the small sample size in RCT studies may introduce bias. These limitations highlight the need for more targeted clinical trial designs specifically for leukemia sub-types.

Selenium holds significant promise as an anti-cancer agent, but its clinical utility depends on careful consideration of form, dose, and individual variability. This systematic review highlights strong preclinical evidence supporting the potential of selenium as a therapeutic agent in leukemia [7]. *In vitro* and *in vivo* studies have consistently shown that selenium induces apoptosis, disrupts the cell cycle and modulates the MAPK/ERK and PI3K/Akt pathways [21], with ROS generation playing a key role [7]. Selenium enhances chemotherapy effects and protects normal lymphocytes. Clinically, pediatric trials have reported improved immune marker levels and symptom relief; however, the results in adults are inconclusive, with no consistent cytokine modulation. Selenium is safe and well tolerated, even at 400 µg/day, but clinical studies lack power and standardized protocols [7]. Overall, selenium is a promising adjunct therapy, and future well-designed trials are needed to confirm its efficacy and determine its role in leukemia treatment. Critical appraisals of the literature are presented in Supplementary Table S1 which has been excluded from the main text for the sake of brevity.

Limitations

To our knowledge, this is the first comprehensive review on this topic for leukemia. Since not all studies have information on standard errors, variances, confidence intervals, we cannot quantify effect sizes. However, our approach of analyzing an emerging therapy may be useful for broader cancer fields like precision medicine.

Preclinical studies have shown consistent selenium-induced anti-leukemic effects across diverse models and leukemia subtypes, as validated through transcriptomics, flow cytometry, and redox modulators. Animal experiments and drug combinations bolster its therapeutic potential. However, the clinical data remain inconclusive due to the small sample sizes, varied outcomes, and lack of leukemia-specific endpoints, such as remission rate, minimal residual disease (MRD), and overall survival. The benefits observed from an immunological standpoint may not solely be applicable to specific leukemia subtypes. We would like to emphasize the importance of leukemia-specific trial design by stratification for a disease subtype. Notably, Evans et al. reported no significant biomarker changes, underscoring the need for larger, targeted trials [34]. Lastly, this review focused only on English-language peer-reviewed publications.

Implications for research/clinical practice and future research

Selenium exhibits low toxicity, targets multiple cancer-related pathways, and may enhance chemotherapy tolerability—making it a

promising adjunct in leukemia treatment. However, its clinical utility still requires rigorous validation. Therefore, future research priorities include:

Design leukemia-specific RCTs.

Standardize selenium formulations, dosing regimens, delivery systems (e.g., nanoparticles) and pharmacodynamic endpoints of interest.

Standardize established clinical endpoints (e.g., remission rates, survival, MRD and treatment related toxicities).

Investigate selenium–drug interactions using pharmacodynamic studies.

Identify predictive biomarkers, such as seleno-protein expression or redox profiles.

Use of selenium in chimeric antigen receptor T-cell (CAR-T) therapy contexts.

Conclusion

Selenium, an essential micronutrient, has emerged as a promising candidate in cancer prevention and therapy due to its antioxidant, immunomodulatory, and pro-apoptotic properties. This detailed review synthesizes findings from key studies, including clinical trials and mechanistic research, to evaluate its therapeutic potential for leukemia. We discuss various forms of selenium, their biological activities, and the implications for personalized medicine and nanotechnology-based delivery systems. Most existing trials were concerned with inflammatory cytokines, immunological markers, and symptom relief and not specifically related to outcomes in leukemia treatment.

Preclinical data have shown that selenium promotes apoptosis and enhances the effects of chemotherapy in leukemia. Early clinical studies support its safety and immunological benefits; however, its direct anti-leukemic efficacy in humans remains unproven, and robust clinical trials are needed for validation. Hopefully, this review can become a useful resource for researchers to plan future studies. We recommend core clinical endpoints for future trials for remission rates, MRD, overall survival, and treatment-related toxicity. Also, it is very important to emphasize the need for standardization of selenium formulations, dose regimens, and pharmacodynamic endpoints of interest.

References

1. Choi HS, Kim BS, Yoon S, Oh SO, Lee D. Leukemic Stem Cells and Hematological Malignancies. *Int J Mol Sci.* 2024;25(12):6639. Available at: https://doi.org/10.3390/ijms25126639
2. International Agency for Research on Cancer. Global Cancer Observatory: Cancer Today. Lyon, France: IARC;2022. Available at: https://gco.iarc.fr/today
3. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin.* 2021;71(3):209–249. Available at: https://doi.org/10.3322/caac.21660
4. Bai S, Zhang M, Tang S, et al. Effects and Impact of Selenium on Human Health, A Review. *Molecules.* 2024;30(1):50. Available at: https://doi.org/10.3390/molecules30010050
5. Shahidin, Wang Y, Wu Y, et al. Selenium and Selenoproteins: Mechanisms, Health Functions, and Emerging Applications. *Molecules.* 2025;30(3):437. Available at: https://doi.org/10.3390/molecules30030437
6. Filippini T, Fairweather-Tait S, Vinceti M. Selenium and immune function: a systematic review and meta-analysis of experimental human studies. *Am J Clin Nutr.* 2023;117(1):93–110. Available at: https://doi.org/10.1016/j.ajcnut.2022.11.007
7. Sewell DG, Bapat P, Boylan LM, Spallholz JE. In vitro Cytotoxic Effects of Control and Selenium Conjugated Transferrins against Leukemia Cell Lines K562 and THP-1. *BJSTR*. 2019;13(3):9984–9995. Available at: https://doi.org/10.26717/BJSTR.2019.13.002402
8. Office of Dietary Supplements, National Institutes of Health. Selenium – Health Professional Fact Sheet. *Office of Dietary Supplements*. 2021. Available at: https://ods.od.nih.gov/factsheets/Selenium-HealthProfessional/
9. Azarm T, Fazilati M, Azarm H, Azarm A. Serum selenium levels in chronic lymphocytic leukemia. *Adv Biomed Res.* 2013;2(1):44. Available at: https://doi.org/10.4103/2277-9175.114177
10. Rocha KC, Vieira ML dos S, Beltrame RL, et al. Impact of Selenium Supplementation in Neutropenia and Immunoglobulin Production in Childhood Cancer Patients. *J Med Food.* 2016;19(6):560–568. Available at: https://doi.org/10.1089/jmf.2015.0145
11. Gandhi UH, Kaushal N, Hegde S, et al. Selenium Suppresses Leukemia through the Action of Endogenous Eicosanoids. *Cancer Res.* 2014;74(14):3890–3901. Available at: https://doi.org/10.1158/0008-5472.CAN-13-3694
12. WEISBERGER AS, SUHRLAND LG. Studies on Analogues of L-Cysteine and L-Cystine. *Blood.* 1956;11(1):19–30. Available at: https://doi.org/10.1182/blood.V11.1.19.19
13. He L, Zhang L, Peng Y, He Z. Selenium in cancer management: exploring the therapeutic potential. *Front Oncol.* 2025;14:1490740. Available at: https://doi.org/10.3389/fonc.2024.1490740
14. Jüliger S, Goenaga-Infante H, Lister TA, Fitzgibbon J, Joel SP. Chemosensitization of B-Cell Lymphomas by Methylseleninic Acid Involves Nuclear Factor-κB Inhibition and the Rapid Generation of Other Selenium Species. *Cancer Res.* 2007;67(22):10984–10992. Available at: https://doi.org/10.1158/0008-5472.CAN-07-0519
15. Daeian N, Radfar M, Jahangard-Rafsanjani Z, et al. Selenium supplementation in patients undergoing hematopoietic stem cell transplantation: effects on pro-inflammatory cytokines levels. *Daru.* 2014;22(1):51. Available at: https://doi.org/10.1186/2008-2231-22-51
16. Vieira ML dos S, Fonseca FLA, Costa LG, et al. Supplementation with Selenium Can Influence Nausea, Fatigue, Physical, Renal, and Liver Function of Children and Adolescents with Cancer. *J Med Food.* 2015;18(1):109–117. Available at: https://doi.org/10.1089/jmf.2014.0030
17. Han B, Wei W, Hua F, et al. Requirement for ERK Activity in Sodium Selenite-induced Apoptosis of Acute Promyelocytic Leukemia-derived NB4 Cells. *J Biochem Mol Biol.* 2007;40(2):196–204. Available at: https://doi.org/10.5483/BMBRep.2007.40.2.196
18. Last K, Maharaj L, Perry J, et al. The activity of methylated and non-methylated selenium species in lymphoma cell lines and primary tumours. *Ann Oncol.* 2006;17(5):773–779. Available at: https://doi.org/10.1093/annonc/mdl004
19. Shi K, Jiang Q, Li Z, et al. Sodium selenite alters microtubule assembly and induces apoptosis in vitro and in vivo. *J Hematol Oncol.* 2013;6(1):7. Available at: https://doi.org/10.1186/1756-8722-6-7
20. Shi K, Meng D, Wang Y, Tian W, Zhang Y, An J. ATM/IKK alpha axis regulates the crosstalk between autophagy and apoptosis in selenite-treated Jurkat cells. *Chem Biol Interact.* 2022;367:110178. Available at: https://doi.org/10.1016/j.cbi.2022.110178
21. Li J, Zuo L, Shen T, Xu C, Zhang Z. Induction of apoptosis by sodium selenite in human acute promyelocytic leukemia NB4 cells: involvement of oxidative stress and mitochondria. *J Trace Elem Med Biol.* 2003;17(1):19–26. Available at: https://doi.org/10.1016/S0946-672X(03)80041-X

22. Zeng H. Arsenic Suppresses Necrosis Induced by Selenite in Human Leukemia HL-60 Cells. *Biol Trace Elem Res.* 2001;83(1):1–15. Available at: https://doi.org/10.1385/BTER:83:1:01
23. Selvam AK, Björnstedt M, Misra S. Therapeutic Potential of Selenium Compounds in the Treatment of Cancer. In: Michalke B, eds. *Molecular and Integrative Toxicology*. Springer, Cham;2018:251–269. Available at: https://doi.org/10.1007/978-3-319-95390-8_13
24. Wu S, Bao Y, Ma D, et al. Sodium selenite inhibits leukemia HL-60 cell proliferation and induces cell apoptosis by enhancing the phosphorylation of JNK1 and increasing the expression of p21 and p27. *Int J Mol Med.* 2014;34(4):1175–1179. Available at: https://doi.org/10.3892/ijmm.2014.1854
25. Fang L, Zhang R, Shi L, et al. Protein-Nanocaged Selenium Induces t(8;21) Leukemia Cell Differentiation via Epigenetic Regulation. *Adv Sci.* 2023;10(35):e2300698. Available at: https://doi.org/10.1002/advs.202300698
26. Siddiqa A, Munir R, Faisal M. Antitumor effects of sodium selenite on acute lymphocytic leukemia. *J Cancer Res Ther.* 2021;17(1):266–268. Available at: https://doi.org/10.4103/jcrt.JCRT_147_17
27. Wang S, Geng Z, Shi N, et al. Dose-dependent effects of selenite (Se^{4+}) on arsenite (As^{3+})-induced apoptosis and differentiation in acute promyelocytic leukemia cells. *Cell Death Dis.* 2015;6(1):e1596. Available at: https://doi.org/10.1038/cddis.2014.563
28. Spengler G, Gajdács M, Marć MA, Domínguez-Álvarez E, Sanmartín C. Organoselenium Compounds as Novel Adjuvants of Chemotherapy Drugs—A Promising Approach to Fight Cancer Drug Resistance. *Molecules.* 2019;24(2):336. Available at: https://doi.org/10.3390/molecules24020336
29. Carter BZ, Gronda M, Wang Z, et al. Small-molecule XIAP inhibitors derepress downstream effector caspases and induce apoptosis of acute myeloid leukemia cells. *Blood.* 2005;105(10):4043–4050. Available at: https://doi.org/10.1182/blood-2004-08-3168
30. Hatfield DL, Tsuji PA, Carlson BA, Gladyshev VN. Selenium and selenocysteine: roles in cancer, health, and development. *Trends Biochem Sci.* 2014;39(3):112–120. https://doi.org/10.1016/j.tibs.2013.12.007
31. An JJ, Shi KJ, Wei W, et al. The ROS/JNK/ATF2 pathway mediates selenite-induced leukemia NB4 cell cycle arrest and apoptosis in vitro and in vivo. *Cell Death Dis.* 2013;4(12):e973. Available at: https://doi.org/10.1038/cddis.2013.475
32. Sonaa E, Usha S, Ja In J. An ex vivo study of selenium, genistein on the morphological and nuclear changes in anticancer drug-induced apoptosis in human peripheral blood lymphocytes. *Biofactors.* 2013;39(3):279–293. Available at: https://doi.org/10.1002/biof.1069
33. Anjum S, Hashim M, Imran M, et al. Selenium Nanoparticles in Cancer Therapy: Unveiling Cytotoxic Mechanisms and Therapeutic Potential. *Cancer Rep.* 2025;8(6):e70210. Available at: https://doi.org/10.1002/cnr2.70210
34. Evans SO, Jacobson GM, Goodman HJB, Bird S, Jameson MB. Comparison of three oral selenium compounds in cancer patients: Evaluation of differential pharmacodynamic effects in normal and malignant cells. *J Trace Elem Med Biol.* 2020;58:126446. Available at: https://doi.org/10.1016/j.jtemb.2019.126446
35. Lü J, Jiang C, Hu H. Selenium compounds for cancer prevention and therapy – human clinical trial considerations. *Med Rev.* 2025;5(3):203–230. Available at: https://doi.org/10.1515/mr-2024-0065
36. Urbano T, Wise LA, Fiore G, Vinceti M, Filippini T. Effects of Selenium Administration on Blood Lipids: A Systematic Review and Dose–Response Meta-Analysis of Experimental Human Studies. *Nutr Rev.* 2025;84(3):551–570. Available at: https://doi.org/10.1093/nutrit/nuaf049
37. Filippini T, Urbano T, Grill P, et al. Human serum albumin-bound selenium (Se-HSA) in serum and its correlation with other selenium species. *J Trace Elem Med Biol.* 2023;79:127266. Available at: https://doi.org/10.1016/j.jtemb.2023.127266