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Systematic Review

Advances in Nanotechnology for Enhanced Leukemia Therapy: A Systematic Review of *In Vivo* Studies

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ABSTRACT

Introduction: Leukemia, a heterogeneous group of blood cancers, can present a significant clinical challenge due to its varying subtypes and complexity. The application of nanotechnology has the potential to revolutionize the treatment of leukemia. Based on *in vivo* studies, this systematic review provided an accurate and current assessment of nanotechnology therapeutic advances in leukemia treatment.
Materials and methods: The present systematic review focused on *in vivo* studies investigating the therapeutic potential of nanotechnology for leukemia treatment. Comprehensive searches were conducted across significant databases, including PubMed, Scopus, and Google Scholar, to identify relevant publications. Selection criteria encompassed studies that employed animal models to assess nanotechnology effects on leukemia progression. Data extracted from selected articles were rigorously analyzed. This review included studies published between 2010 and 2022.
Results: Based on the inclusion criteria, 24 relevant studies were identified. According to the findings of this review, nanotechnology has made substantial progress in the treatment of leukemia, as demonstrated by *in vivo* studies. Advanced nanoparticle-based drug delivery systems, precision gene therapies, and targeted therapeutic approaches have consistently exhibited superior outcomes in treating various leukemia subtypes in animal models. These compelling results emphasize the transformative potential of nanotechnology for leukemia therapy.
Conclusion: In summary, the meticulous analyses of the *in vivo* studies underscore the role that nanotechnology plays in the advancement of the treatment of leukemia. Nanotechnology has demonstrated efficacy in preclinical models, indicating that it can be translated into clinical applications, offering new avenues for treating leukemia and reinforcing its position as an innovative therapeutic approach.

1. Introduction

The term leukemia refers to a group of malignant diseases originating from hematopoietic stem cells and manifesting as anemia, infection, bleeding, and other symptoms. A variety of blood diseases are collectively referred to as leukemia[1]. Leukemia contains many types. According to development speed, leukemia is mainly divided into acute and chronic leukemia. Leukemia is classified primarily into lymphoid and myeloid leukemias based on the type of cells it contains[2]. In recent years, evidence has accumulated that some infectious agents are capable of causing anti-tumor effects against different types of cancers, such as *Toxoplasma gondii*, *Trypanosoma cruzi*, *Trichinella spiralis*, and *Echinococcus granulosus*[3-6]. Acute Lymphocytic Leukemia (ALL) is caused by abnormal

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proliferation of lymphocytes in the bone marrow[7]. According to bone marrow cell morphology and French-American-British classification, ALL is divided into L1, L2, and L3 subtypes. Small lymphocytes dominate Type L1, and the cell size is relatively uniform. Large lymphocytes of different cell sizes characterize type L2. Type L3 occurs predominantly on large lymphocytes with honeycomb-shaped cytoplasm and vacuoles and is relatively uniform in size[8]. If left untreated, these lymphocytes can quickly spread to the circulatory system and other vital organs. The pathogenesis of Acute Myeloid Leukemia (AML) involves the abnormal proliferation and differentiation of a clonal population of myeloid stem cells. According to the different cell types involved, it is divided into seven subtypes, M1–M7[9].

The abnormal differentiation of bone marrow cells reduces the number of differentiated red blood cells, platelets, and white blood cells[10]. Acute Myeloid Leukemia is characterized by malignant, poorly differentiated bone marrow cells accumulating in the bone marrow and peripheral blood but less in other organs[11]. Chronic Myeloid Leukemia (CML) is a form of myeloproliferative disease characterized by the presence of the Philadelphia chromosome and the BCR/ABL fusion gene[12]. According to the World Health Organization (WHO) committees, CML is divided into two phases: the accelerated phase and the blast phase. The clinical symptoms of CML include anemia, increased peripheral blood granulocytes, joint pain, low fever, susceptibility to viral infection, and thrombocytopenia; it is a slow-moving disease that is difficult to treat[13]. Approximately 50% of CML patients present with incidental findings in asymptomatic patients[14]. Furthermore, even in symptomatic patients, the symptoms are mainly nonspecific. The symptoms range from dyspnea upon exertion or fatigue caused by anemia to left upper quadrant pain and early satiety caused by splenomegaly[15]. 5% of patients may also suffer from headache, retinopathy, and vertigo symptoms due to hyperviscosity syndrome resulting from large-scale leucocytosis. Imatinib, a tyrosine kinase inhibitor, is the most widely used CML treatment. Tyrosine kinase inhibitor, however, do not provide a cure[16]. Instead, a bone marrow transplant is required. Drug resistance and cancer relapse further complicate current treatment protocols. Therefore, combining new agents with existing ones offers a promising prospect for treating cancer cells' resistance to drugs, recurrence, and, importantly, a cure without transplantation. One of these strategies, nanotechnology, is emerging as a possible new approach to treating CML[17].

Nanotechnology has recently been developed as a delivery system for pharmaceuticals [18]. A nanosystem is characterized as having a size ranging from 1 to 1000 nm[19]. In the 1990s, nanomedicine was introduced to the medical field[20]. Using nanotechnology, it is possible to encapsulate and distribute hydrophobic compounds that are difficult to administer freely while enhancing their solubility and biocompatibility. Nanosystem materials must be biocompatible, non-toxic, biodegradable, and sufficiently stable to be administered *in vivo*[21]. Similarly, nanomaterials can be used as micro-spectroscopy contrast agents or labels, facilitating rapid, specific, and sensitive diagnostics and determining the presence of minimal residual diseases (MRDs) following treatment[22]. With their large surface area, they can be loaded with several therapeutic drugs and stealth agents, targeting elements, triggering strategies, magnetic properties, and imaging characteristics[23]. The multifunctional trait of nano-delivery complexes has been most studied in developing a theranostic (therapeutic + diagnostic) strategy for attacking cancer by integrating a variety of drug agents with imaging probes to monitor and scan the therapeutic agents distributed throughout the body[24]. Theranostics provides real-time evaluation of cancer cell growth or spoilage. Non-viral nanoparticle delivery methods, however, are still experimental[25]. Several issues need to be addressed, including side effects, controlled release, targeted therapy, and combinatorial therapy. Using nanoparticles as drug delivery systems is a promising strategy for combating resistance[26]. This review discusses recent developments in organic nanomedicine, organic nanoparticle chemical properties, and their clinical applications in cancer treatment.

2. Materials and Methods

This systematic review methodology used SID, MagIran, IranMedex, IranDoc, Google Scholar, ScienceDirect, Scopus, PubMed, and Web of Science (ISI) databases. These databases were searched, and relevant publications were selected based on plausible keywords: prevalence, curcumin, *in vivo* studies, and cancer. The search included studies published between 2010 and 2022, written in English, and involving *in vivo* animal experiments. The following search terms were used: "Nanotechnology," "Metal Nanoparticles," "Leukemia cancer," and "*in vivo*." A standardized form was used for data extraction, including the following variables: study characteristics (authors, publication year, study design), experimental details (animal model, treatment duration), outcomes of interest (tumor size, apoptosis rates, molecular pathways), and adverse effects. Two independent reviewers performed this process, and any contradictions were resolved by agreement. Among 760 articles reviewed in the literature from 2010 to 2022, 114 articles met the eligibility criteria and were included in the current systematic review. Data unpublished, duplicated papers, and abstracts of congress proceedings were excluded. Upon removing duplicates and screening the articles for eligibility, 24 articles were included in the quantitative synthesis (Figure 1).

3. Metallic nanoparticles

A variety of metals and their oxides have been used to produce nanoparticles (NPs), including silver (Ag), aluminum (Al), iron (Fe), gold (Au), silica (Si), copper (Cu), zinc (Zn), manganese (Mn), cerium (Ce), titanium (Ti), platinum (Pt), or thallium (TI)[27]. In general, nanoparticles are synthesized via two approaches, namely a top-down approach and a bottom-up approach. Top-down

approaches for the synthesis of nanoparticles include lithography, laser ablation, ball mining, sputtering, electro-explosion, and etching. Bottom-up synthesis is the most effective method for generating NPs since simpler molecules are used to prepare the NPs[28]. The green synthesis approach is considered the most economical, sustainable, reliable, and eco-friendly approach to synthesizing NPs[29]. The synthesis of NPs in this manner does not require toxic chemicals, high temperatures, or high pressures; it is also not harmful to human health or the environment[30]. The method is also considered preferred for fabricating NPs because it utilizes low-cost and non-hazardous raw materials such as microorganisms fungi[31], algae[32], bacteria[33], plant extracts[34], natural polymers, and proteins[35]. Proteins, polysaccharides, sugars, amides, ketones, aldehydes, and carboxylic acids are among the biomolecules present in these resources, along with various phytochemicals, such as terpenes, alkaloids, and polyphenols, including flavonoids, which facilitate immediate reduction. Alternatively, the chemical route uses toxic reducing agents, which limit their biomedical potential and threaten the environment. The biological approach resolves this issue by using safe reducing agents and could be utilized in cancer therapeutics[36,37].

4. Nanoparticles for cancer therapy

Radiation therapy, chemotherapy, immunotherapy, photodynamic therapy, cancer vaccinations, stem cell therapy, and surgery are some of the treatments available at present. However, these treatment options have severe side effects and pharmacokinetic issues[38,39]. Research on nanoparticles is becoming increasingly attractive as a means of overcoming these challenges[40]. The large surface-to-volume ratio of nanoparticles is responsible for their interaction with biological systems, as at the cellular level, the atoms are available for various reactions to occur[41,42]. The unique morphology of NPs influences their insertion or entry into cells[43]. Surface charges of nanoparticles affect their circulation time in the bloodstream and rate of uptake and translocation[44]. Comparatively to anionic NPs, cationic nanoparticles appear to damage plasma membrane integrity, impair organelle architecture, and disturb normal cellular function[45]. Thus, cationic NPs often exhibit a higher rate of non-specific uptake than neutral or negatively charged NPs[46]. There is, however, a shorter blood circulation time for neutral and negatively charged NPs, which reduces their bioavailability[41]. Positive groups, such as primary amines, present on the surface of polystyrene microparticles have previously been reported to facilitate faster cell internalization than microparticles bearing hydroxyl, sulfate, and carboxyl groups[47]. Additionally, mesoporous silica nanoparticles with amine groups have been used as gene delivery tools *in vitro* and *in vivo*. They demonstrated improved internalization because of the positive groups on their surfaces[48].

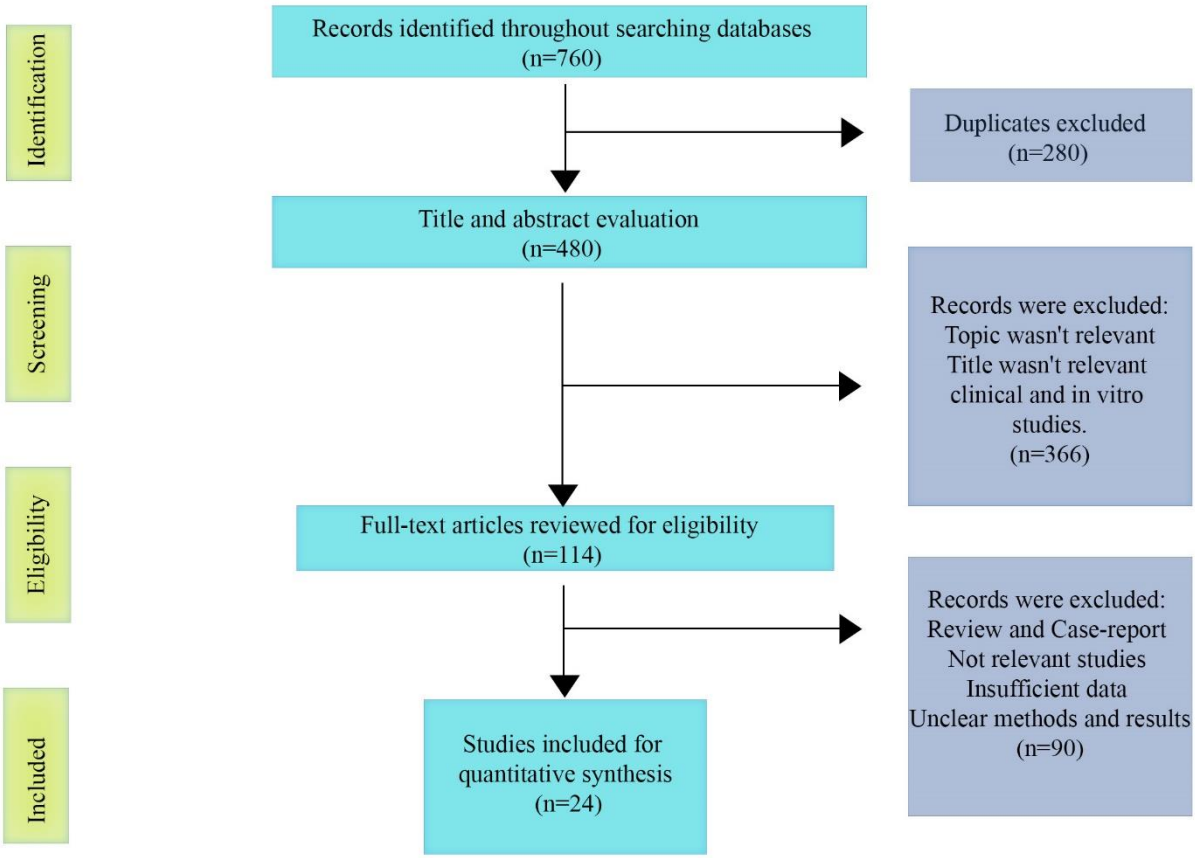

Figure 1. The methodology of the systematic review for extracting information

It becomes increasingly apparent that NPs are attracting significant interest as carriers for diagnostics, hydrophobic medicine hyperthermia, therapeutics, as well as the delivery of antineoplastic drugs and agents to tumor tissues, as the delivered NPs can penetrate deeply and provide the drug to a specific target area [49]. Nanoparticles in cancerous cells have been reported to enhance the intracellular concentration of drugs, either by active or passive targeting, while minimizing toxicity to normal cells[50]. Further, NPs have been developed as temperature or pH-sensitive carriers for targeted drug delivery[51]. These nanoparticles can deliver and release drugs within the tumor area through ultrasound waves or magnetic fields as a temperature-sensitive drug delivery system[52]. In the acidic environment of cancerous cells, the pH-sensitive system can carry and release drugs efficiently[53]. Additionally, these NPs can be modified with specific targeting moieties, including antibody fragments, antibodies, particular molecules, RNA aptamers, and small peptides that enhance their ability to bind selectively to cancerous cells and tissues[54]. Angiogenesis plays a crucial role in tumor progression towards metastasis[55]. Due to an increased expression of angiogenic factors, cancer cells display abnormal membrane structure[56]. Anti-angiogenic nano-targets could be delivered into the tumor microenvironment using this dysregulated membrane architecture to inhibit excessive angiogenic stimulator production[57]. Due to its effectiveness, several studies have reported that it blocks the signaling of Vascular endothelial growth factor (VEGF), Platelet-derived growth factor (PDGF), endothelial differentiation gene receptor, and angiopoietin, critical neovascularization components [58]. Anti-angiogenic nanotherapeutics are highly effective in delivering drugs with short half-lives, poor oral availability, and poor distribution within tumors[59]. Nanoparticles, depending on their size, can easily penetrate the tumor microenvironment and exert an antiangiogenic effect[60]. Nanoparticles with optimum sizes can intrinsically approach metastasized tumors and release drugs efficiently through enhanced permeability and retention (EPR)[61].

5. Nanomedicine as a novel approach to combat leukemia

Nanotechnology has contributed significantly to the advancement of medicine[62]. The use of nanoparticles as an enhanced drug delivery vehicle on current platforms has been demonstrated to improve selectivity and increase drug delivery[63]. Further, nanomaterials provide more accessible control over the behavior of drugs once they have entered the patient's body due to their ability to manipulate properties, such as tiny size, targeting ability, high loading capacity, and sustained release pattern. This results in a higher level of selectivity and bioavailability of the drug at the target site and a decrease in adverse side effects[64]. As early as the 1990s, nanomedicines have been incorporated into approved cancer therapies due to their apparent advantages[65]. Several nano-formulations have been developed to deliver chemotherapeutic drugs (mitoxantrone and flavopiridol) to leukemia cells[66]. Using NPs has demonstrated that nanoscale can increase the circulation half-life and bioavailability of these drugs, reduce their renal clearance, and decrease average tissue exposure to high concentrations[67]. Accordingly, nanoformulations could enhance the solubility of flavopiridol, act as a barrier to its interaction with plasma proteins, and eliminate the toxic effect of flavopiridol formulations on non-targeted cells[68,69]. Nanometals display cytotoxic effects that selectively inhibit cancer cell growth, as mentioned in some literature, despite their synergistic capacity to enhance the efficacy of other drug products[70,71]. In leukemia, these applications have begun to attract attention, with most efforts focused on biogenic silver (Ag) and gold (Au) nano-structures. In recent studies, biogenic nanoparticles have shown promising anti-cancer properties[72,73].

5.1. Silver nanoparticles for leukemia therapy

Silver nanoparticles (AgNPs) have promising anti-tumor effects. A low concentration of AgNPs has been reported to cause DNA damage and chromosomal aberrations (genotoxicity), but no significant cytotoxicity has been observed[74]. However, Durán et al.[75] found no genotoxicity effects for different human culture cells treated with up to 10 mg/mL of capped AgNPs (diameter 6–80 nm). Several toxicological studies have been conducted on nanoparticles, which may lead to a negative perception of their use[76,77]. Nevertheless, toxicity itself can be helpful in cancer therapies because it is highly sought after. Positive outcomes have been achieved when incorporating AgNPs into cancer treatments[78]. Cells not only passively interact with them but can regulate their functions actively through molecular processes[79]. Due to their exceptional properties, silver nanoparticles (AgNPs) have been demonstrated to be one of the most effective antimicrobial and anti-cancer agents among various biosynthesized metallic and metal oxide nanoparticles[80]. By exposing cells to AgNPs, the most notable outcomes include arresting the respiratory chain of the cells, influencing cell division through membrane damage, and inducing numerous subordinate effects, which include the production of Reactive Oxygen Species (ROS), gene modification, enhancement of apoptosis or necrosis, and an increase in oxidative stress and mitochondrial damage[٨١-٨٣]. Additionally, their protective effect against bacterial, fungal, and viral infections could be very desirable during chemo- and radiotherapies due to the decreased immunological resistance of cancer patients[٨٤].

5.2. Gold nanoparticles for leukemia therapy

Gold nanoparticles (AuNPs) have been introduced as promising agents for cancer therapy that may be used as drug carriers, photothermal agents, contrast agents, and

radiosensitizers [85,86]. Silver nanoparticles cytotoxic effect is caused by the interaction between gold atoms and the functional groups of intracellular proteins, phosphate groups, and nitrogen bases in DNA[^Y]. Laskar et al.2020 investigated the use of Hibiscus sabdariffa, also known as roselle, for the biosynthesis of AuNPs[^^]. Polyphenolic agents in high concentrations in crude and pure extract compounds provide excellent anti-cancer properties, including selective cytotoxicity, apoptosis, cell cycle arrest, anti-metastasis, and autophagy[88]. This study confirmed the nanosystem's therapeutic activity against the AML rodent model. The *in-vitro* results showed that AuNPs decreased the viability of the cells in a dose-dependent manner against three different cancer cell lines (Murine C1498, Human HL-60/VCR, and 32D-FLT3-ITD cell lines) without any cytotoxicity to Human umbilical vein endothelial cells (HUVEC) cell line. The results of *in vivo* experiments revealed that mice treated with AuNPs showed comparable effects to DOX via reducing the pro-inflammatory cytokines and the total white blood cells, blast, monocyte, neutrophil, eosinophil, and basophil counts, and also enhancement of the anti-inflammatory cytokines and the platelet, lymphocyte, and RBC parameters in comparison to the control[89]. The results of a recent study revealed the potential use of these plant-synthesized AuNPs as potential antileukemic agents[90]. The anti-cancer activity of the synthesized nano-structure was compared with DOX in mice models with AML. FTIR results confirmed the reducing property of the antioxidant compounds in the extract, which were used for AuNP fabrication. The fabricated NPs had low cell viability and dose-dependent toxicity against different types of leukemia cell lines. Similar to previous results, these NPs enhanced the amounts of anti-inflammatory cytokines, lymphocyte, platelet, and RBC parameters and reduced the weight and volume of the liver and spleen, the pro-inflammatory cytokines, and the total WBC compared to untreated mice[91]. The anti-cancer activity of biosynthesized AuNPs against leukemia was also compared with mitoxantrone. In detail, AuNPs with a mean size of about 25 nm were synthesized using an extract of aqueous *Lens culinaris* (*L. culinaris*) seed. Different features of these NPs were then compared with those of mitoxantrone. It was confirmed that both had the same *in vitro* antioxidant and anti-cancer activities against leukemia cancer cells and could decrease the volume and weight of the spleen, liver, total WBC, and pro-inflammatory cytokines *in vivo*. Additionally, they increased the expression of sphingosine-1-phosphate receptor-5 and sphingosine-1-phosphate receptor-1 mRNAs and anti-inflammatory cytokines *in vivo*. These results revealed that these biosynthesized AuNPs could be used either in combination with chemotherapeutic drugs or instead of them[92,93].

5.3. Zinc and zinc oxide nanoparticles as anti-cancer therapeutic

Recently, the biological synthesis of zinc and zinc oxide nanoparticles (Zn/ZnO-NPs) has attracted much attention due to phytochemical components such as flavonoids, phenolics, and alkaloids[94,95]. It is believed that the specific physicochemical properties of ZnO NPs contribute to their cellular uptake[96]. Their innate toxic properties against cancerous cells generate intracellular ROS, ultimately resulting in apoptosis. These characteristics make them an attractive candidate for biomedical applications. Different parts of the plant have been extensively studied for the biosynthesis of ZnO NPs, and their anti-cancer effects have been investigated *in vitro* using various cancer cell lines[97]. Spherical and hexagonal-shaped bio-extract-derived Zn NPs show cytotoxicity in lung cancer cell lines A549 and Calu-6[98]. These NPs exhibited different sizes and IC50 values based on the types of plant extracts used for their preparation and the doses administered [99,100]. Spherical and hexagonal biosynthesized ZnNPs with sizes ranging between 22.5–50 nm, prepared from diverse plant extracts, inhibited WEHI-3 leukemia cancer cell lines, with IC50 values ranging between 2.25–12.4 μg/mL[98]. Spherical biosynthesized ZnNPs of cell lines and their IC50 values varied dose-dependently and depended on the type of plant extract used[101]. The biosynthesized hexagonal ZnNPs with sizes 10 ± 1.5 nm showed inhibitory actions against CaOV-3 ovarian cancer cell lines with an IC50 value of 10.8 ± 0.3 μg/mL. Inhibition by biosynthesized spherical ZnNPs of 47 nm size was observed against colon cancer cell lines HT-29 with 9.5 μg/mL IC50 value, respectively[98]. Similarly, the biosynthesized ZnO-NPs showed potential inhibitory activities against epidermoid carcinoma cell lines A43 with an IC50 value of 16.5 ± 1.6 μg/mL and against liver cancer cell lines Hep-G2 with an IC50 value of 14.1 ± 0.7 μg/mL[98,102].

5.4. Copper/Copper oxide nanoparticles as anti-cancer therapeutics

Copper/Copper oxide nanoparticles (Cu/CuO-NPs) have attracted significant attention as cytotoxic nano-entities due to their low cost, ease of availability, and similar properties to noble metals[103]. Because of their highly effective light-to-heat transformation properties under near-infrared laser irradiation, copper and copper oxide nanoparticles are extensively used in cancer imaging[104]. Different biologically synthesized Cu/CuO NP have been shown to be cytotoxic against multiple cancerous cell lines. Plant-mediated biosynthesized CuO NPs, spherical and hexagonal with 26.6 nm sizes, exhibited inhibitory actions against cervical cancer cell lines HeLa by initiating ROS-mediated apoptotic pathways[105]. Similarly, spherically shaped CuO NPs of 12 nm sizes, prepared from aqueous leaf extracts of different plants, showed cytotoxicity against cervical cancer cell lines HeLa, breast cancer cell lines MCF-7, and lung cancer cell lines A549, and their IC50 values varied depending on the types of plants used[106]. Inhibition of MCF-7 breast cancer cell lines was performed using biosynthesized spherically shaped CuO NPs of 26–30 nm sizes with a 56.16 μg/mL IC50 value[107]. In another study, aqueous leaf extract-derived CuO NPs, which are spherical with sizes ranging between 20–50 nm, showed the highest

anti-cancer activity against AMJ-13 breast cancer cell lines with an IC50 value of 1.47 µg/mL and against SKOV-3 ovarian cancer cell lines with a 2.27 µg/mL IC50 value[108]. Biosynthesized CuO NPs with 577 nm sizes displayed cytotoxicity against lung cancer cell lines A549 through apoptosis initiated via nuclear fragmentation and showed an IC50 value of 200 µg/mL[109]. Similarly, spherically shaped CuO NPs of different sizes were tested against cervical cancer cell lines HeLa and lung cancer cell lines A549[110]. Spherically shaped biosynthesized CuO NPs of about 4.8 nm were tested for cytotoxicity against prostate cancer cell lines PC-3[111] (Figure 2).

This comprehensive figure illustrates the multifaceted roles of nanoparticles in cancer therapy, focusing on Silver Nanoparticles (AgNPs), Gold Nanoparticles (AuNPs), Zinc and Zinc Oxide Nanoparticles (Zn/ZnO-NPs), and Copper and Copper Oxide Nanoparticles (Cu/CuO-NPs). The top left section delves into the Genotoxicity Debate surrounding AgNPs, presenting conflicting evidence on their impact on DNA and chromosomes. The Dual Role of AgNPs in Cancer Therapy is highlighted, emphasizing both active mediation of molecular processes and passive interaction with cells. Moving to AuNPs, their Versatile Applications are depicted, showcasing their functions as drug carriers, photothermal agents, contrast agents, and radiosensitizers. Physicochemical Interactions with intracellular proteins/DNAs are illustrated, underlining their cytotoxic effects on cancer cells. *In Vivo* Therapeutic Activity of plant-synthesized AuNPs is compared with doxorubicin in a rodent model of acute myeloid leukemia. The bottom sections explore the Biological Synthesis of Zn/ZnO-NPs, their cytotoxicity against various cancer cell lines, ROS Generation, and Induction of apoptosis. Lastly, the cytotoxicity and ROS-mediated apoptosis of Cu/CuO-NPs are presented, along with their applications in cancer imaging and inhibitory actions against specific cancer cell lines.

6. *In vivo* models

Nanoformulations enhance biomarker detection, providing more straightforward assays with higher sensitivity[112]. Additionally, nanomedicines have been shown to improve the efficacy-toxicity ratio of anti-cancer agents, which enables the monitoring of liquid tumor diagnosis and treatment in real time[64]. Nanomedicines, however, depend heavily on the availability of *in vivo* tumor models that closely mimic the environment where actual human tumors grow[113]. There are several obstacles to developing leukemia/lymphoma models since the pathogenesis of the disease in murine models is not relevant to most human cases; in addition, these models do not reflect the complex microenvironment in which these human cancers develop, nor do they reflect their genetic and molecular heterogeneity[114,115]. Using xenografts mitigates some of these issues; however, they are usually conducted on immunocompromised mice to avoid immune rejection of human cells, excluding the immune system's effect on tumor expansion and NP efficacy[116]. The variability of experimental conditions between different preclinical studies using NPs to fight leukemia and lymphoma contributes to their decreased clinical impact[64]. For clinical translation of nanoscale diagnostic assays and treatments, standardized manufacturing procedures and controls need to be recognized by regulatory agencies such

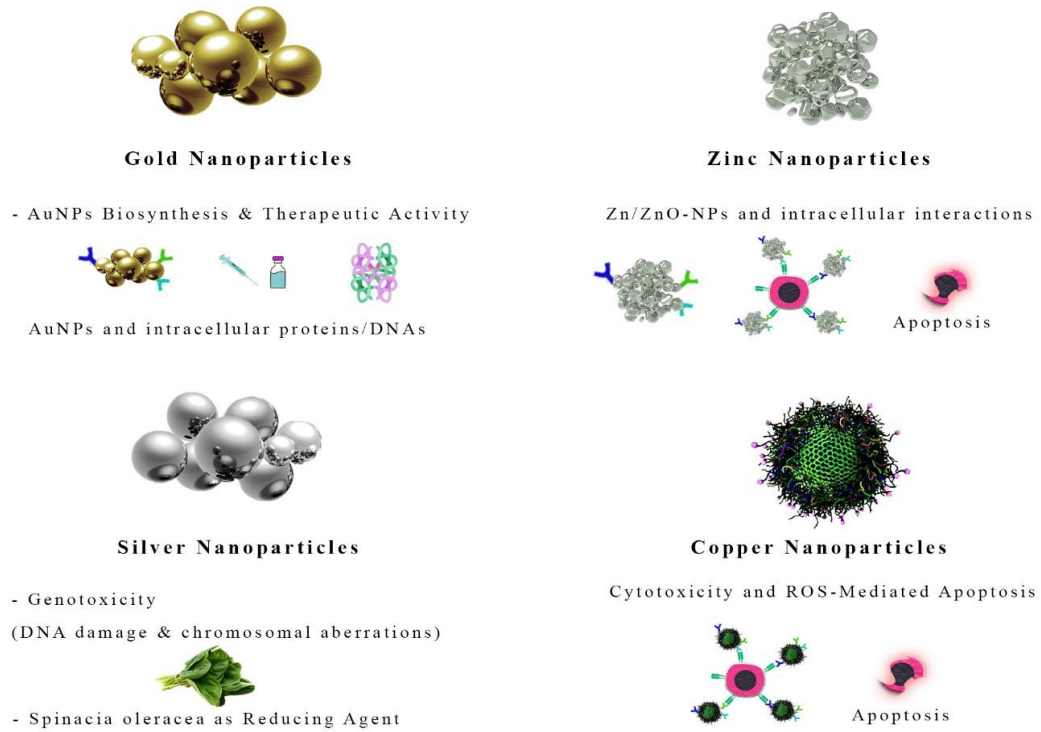

Figure 2. Nanoparticles in leukemia therapy- mechanistic insights and therapeutic applications

as the US Food and Drug Administration (FDA) or the European Medicines Agency[117]. Moreover, there needs to be more *in vivo* toxicity, stability, and biodistribution studies essential to evaluating nanoparticles as delivery vehicles, imaging agents, or therapeutic agents[118,119].

Several studies aim to mimic tumor characteristics using *in vivo* models[120,121]. Their significance for cancer research lies in knowing cancer biology to develop new therapies. Different animal models have been established as notable tools for studying human cancers, providing valuable information on cancer biology, evaluating upcoming anti-tumor therapies, discovering target molecules, and validating biomarkers[122]. Current research looks at a broad spectrum of cancers to understand their biological behavior. Consequently, animal models need to include relevant characteristics of the tumor, such as its microenvironment, anatomy, natural history, angiogenesis, and metastasis. Further, animal models are essential for understanding antineoplastic drug pharmacokinetics, metabolism, and distribution[123,124]. Technological advances in genetic and cancer tissue engineering offer enormous preclinical information potential. Considering the most recent advances in *in vivo* models using MNPs provides a valuable platform for evaluating nanomedicine in preclinical studies[125]. This review focuses on the soil nematode *Caenorhabditis elegans* (*C. elegans*), the freshwater fish *Danio rerio* (*D. rerio*), known as Zebrafish, and the murine model.

6.1. Caenorhabditis elegans, and Danio rerio Models

C. elegans and zebrafish models have been used to understand fundamental biological processes involved in cancer, such as apoptosis, proliferation, angiogenesis, invasion, metastasis, genome instability, and metabolism[126]. Considering that *C. elegans* shares a high homology with human genes, it offers a powerful platform for studying carcinogenesis and identifying new cancer drug targets. Many biological processes, including apoptosis, cell signaling, cell cycle, cell polarity, metabolism, and aging, are conserved between *C. elegans* and mammals[121]. Zebrafish is a valuable model widely used to study developmental biology and cancer. The evolutionary conservation of cancer-related genes between humans and Zebrafish is surprising and allows the results obtained in fish to be extrapolated to humans. Zebrafish are a reliable model for studying human cancer[127]. Recent xenotransplantation studies in Zebrafish have shown to be adequate for evaluating the invasiveness of patient-derived xenograft cells. In addition to their significant conservation of genes, these organisms make excellent models for genetic, molecular, and biochemical studies[128]. For instance, studies exposing larval-stage nematodes to AuNPs revealed several differentially expressed genes. Most were upregulated and involved in amyloid processing, citrate cycle, clathrin-mediated endocytosis, apoptosis, and G-protein signaling[129]. These findings suggested that *C. elegans* AuNPs uptake is achieved by endocytosis via a clathrin coating. AuNP exposure also induced neural damage and feeding behavior changes. Furthermore, mutant animals displayed hypersensitivity to AuNPs. Other studies showed that AuNPs triggered changes in the cellular defense response and lipid catabolic processes of *C. elegans*[130]. Additionally, changes in lipid storage, body morphogenesis, shape, and size were observed. The processes of metal detoxification, homeostasis, and adaptation to stress were likewise modified. They also showed morphological changes in the offspring, locomotion problems, and fertility alterations. On the other hand, when adult zebrafish were exposed to AuNPs for 96 h, gene expression at the lowest concentration was similar to the control. The authors found that down-regulation affects biological processes related to development, biogenesis, metabolic processes, cellular localization, biological adhesion, and locomotion[131].

Studies performed on zebrafish larvae, where AgNPs were exposed for six days post-fertilization, showed no adverse effects on fish survival and growth. Unexpectedly, AgNP exposure resulted in higher survival rates for zebrafish larvae, particularly those with the highest concentration (1 mg/L)[132]. Other studies identified a substantial accumulation of Ag in the liver blood vessels, interstitial tissue, and neural changes after AgNP exposure[131,133]. The overlapping functions were altered when nematodes or Zebrafish were exposed to MNPs, including cell signaling (MAPK signal or G protein), control of cell growth, apoptosis, stress response, and DNA damage[129]. Most of these responses can trigger cancer, demonstrating that these model organisms are beneficial for studying the impact of MNPs at the level of the whole organism. Interestingly, MNPs significantly impact the expression of development and neurogenesis genes. Altering the expression of developmental genes could lead to the misregulation of pathways that can cause malignant formation. *C. elegans* and Zebrafish could be used for future approaches or as a preclinical cancer model alongside mouse use[134].

6.2. The Murine Model

The murine model will be briefly described because it is an excellent organism for studying cancer onset, invasion, and metastasis[135]. It represents a significant step between *in vitro* systems and clinical studies. The mouse genome is highly homologous to the human genome, which can simulate a series of biological characteristics, such as the occurrence, development, and metastasis of human cancer cells *in vivo*[136 137]. Moreover, it has the advantages of convenient feeding, low price, and easy gene modification. It provides an effective tool for cancer research and drug discovery and verification[138]. The most widely accepted animal models in cancer research are syngeneic, genetically modified mouse models (GEMMs), chemically induced models, and xenograft models. Xenografts can be divided based on the source of the tumor: xenografts with conventional cell lines (cell line-derived xenografts, CDX) or with samples obtained from patients with some kind of cancer (patient-derived xenografts, PDX)[139]. In GEMMs, spontaneous tumor initiation occurs within the correct microenvironment from an otherwise normal tissue cell[140].

These may be simple oncogenic-driven transgenic mice. One limitation of conventional GEMM models is that regulatory sequences that drive transgene expression need to be more well-defined in specific lineage/expression domains[122]. Human tumors may not necessarily exhibit the same oncogenes. However, these models are helpful in the study of cancer. This field has turned to more specific models emulating human disease genetics with spatial and temporal activation of oncogenes and deletion of tumor suppressors targeting mouse tissues.

A cell line-derived Xenograft or CDX model is widely applied to test anti-cancer therapies[141]. Human tumor samples are cultured as cell lines and implanted into immunodeficient mice to test the efficacy of anti-tumor compounds *in vivo*[142]. CDX is one of the most straightforward and most commonly used systems based on the engraftment of human cancer cell lines into immunodeficient animals[143]. CDX has proven useful for probing cancer genetics, biological processes, and metastatic potential. However, it has some limitations, including reduced intra-tumoral heterogeneity and low effectiveness in predicting clinical performance[144]. In addition, the lines used are frequently derived from highly aggressive malignant tumors, making them less helpful in modeling early events in the evolution of the primary tumor. Furthermore, in most cases, immunosuppressed animals are required, increasing their care costs. It is also essential to consider the transplant location. Generally, subcutaneous injection (ectopic) and cell implantation in the mouse's specific tissue (orthotopic) are recommended. On the other hand, many studies show that AuNPs and AgNPs obtained by green biosynthesis have cytotoxic or antiproliferative effects on different tumor cells of different types of cancer[145,146]. Despite this, most of these studies have been conducted with *in vitro*-grown cells. *In vivo*, studies of anti-tumor activity are relatively rare. The use of AuNPs and AgNPs *in vivo* should be evaluated as soon as possible since these models are closer to those found in patients with cancer[147]. There have been advances in establishing diagnostic and therapeutic applications for AuNPs and AgNPs synthesized by chemical methods, but it is also necessary to evaluate biogenic nanoparticles[148].

7. Nano-toxicity

Even though they have promising potential in the biomedical field, specific adverse health effects are associated with their use[149,150]. For example, agglomeration poses a significant challenge in translating this therapy into medicines due to its toxic effects on organ systems[151]. It can cause cellular injury even if it is not agglomerated. NPs' toxicity is generally attributed to their morphology and surface reactivity[152]. NPs can be controlled in terms of their toxicity by including free groups at their surfaces, such as -COOH groups, which are considered less toxic than -OH groups and -NH2 groups[153]. Toxicity can also be minimized by controlling metal NP size (30-100 nm)[153]. Understanding the possible interactions between biological systems and nanomaterials is imperative to minimize aggressive reactions when using nanomaterials. As a result of the presence of biocompatible phytoconstituents, biological synthesis of NPs is preferred for reducing toxicity. Additionally, some studies have shown that polyphenol compounds are not toxic to healthy cells while exhibiting toxicity against cancerous cells[154].

7.1. Toxicity of silver nanoparticles

Several possible methods of exposure to AgNPs can affect human health, including dermal contact, oral administration, inhalation, and blood circulation[155]. Macrophages are the first cells AgNPs encounter in the human body[156]. It is known that the size of the AgNP dictates its mode of cytotoxicity to murine macrophages (Ag+ ion-specific and/or particle-specific)[157]. The toxicity of AgNPs (<10 nm) is mainly mediated by released Ag+ ions, with the liver being the major target organ, followed by the spleen, lungs, and kidneys[158]. One study showed that both 20 nm and 100 nm AgNPs on Wistar-derived WU rats treated at 6 mg/kg body weight doses increased spleen weight; additionally, clinical chemistry parameters indicated liver damage[159]. A separate study on AgNP inhalation toxicity showed that AgNPs influenced neutral mucins in the respiratory mucosa of Sprague–Dawley (SD) rats exposed to AgNPs at concentrations of 0.5–61 μg/m3, yet without toxicological significance[160]. Furthermore, another study showed that AgNPs had little effect on the nasal cavity and lungs[161]. According to the study, silver levels reported from nanomaterial-manufacturing workers exposed to concentrations of 0.35–1.35 g/m3 were only 0.0135–0.034 mg/m3 for blood and 0.043 mg/m3 for urine, and there were no significant findings regarding their health status[162]. Although many toxicological studies using AgNPs have been reported, it is still difficult to draw a definite conclusion about their toxicity [76]. Different synthesis methods, their different sizes, the presence or absence of capping agents, various organisms, and/or the types of cultures might result in AgNPs having other toxicological properties. Accordingly, their risks should be evaluated on a case-by-case basis.

8. Future perspectives

The use of active drug targeting to treat leukemia is promising. Associating drugs with antibodies can increase their delivery to cancer cells[163]. Nanoparticles fused with antibodies to deliver targeted drugs are a profitable strategy for active targeting. Bicho et al. 2010 investigated the possibility of directing PLGA nanoparticles to target cells expressing the human CD8 membrane protein, a recognized cellular marker of lymphoblastic leukemia cells[164]. PLGA nanoparticles were prepared using an oil-in-water emulsion and solvent extraction/evaporation technique[165]. The anti-human CD8 antibody was then coupled to the nanoparticles. Nanoparticles in suspension were used to target cells and were shown to reduce side effects associated with unspecific drug uptake into healthy tissues[166]. A promising approach to improving the efficacy

of nanoparticles' active targeting for lymphoblastic leukemia treatment is generated by producing CD8 nanoparticles[164]. Additionally, gelatin nanoparticles crosslinked with glutaraldehyde were used to target anti-CD3 antibodies to T-lymphocytic cells. These nanoparticles were surface-modified by covalent attachment of sulfhydryl groups such as Neutravidin and conjugated with an anti-CD3 antibody[167]. There is potential for receptor-mediated uptake of drugs in target cells using these nanoparticles as drug carriers.

Vascular endothelial growth factor (VEGF) is a significant signaling molecule expressed by bone marrow stromal cells and its receptors (VEGFR) in hematologic malignancies, including leukemia[168]. The role of VEGF signaling in transformation, metastasis, and prognosis is correlated with vascularization and tumor proliferation[168]. Wang et al. (2014) explored the safety and efficacy of chitosan nanoparticle siRNA-VEGF and Flt-1 in leukemic U973 cells and revealed that silencing VEGF and the VEGF receptor Flt-1 are valuable candidates for leukemia treatments, particularly in combination with traditional drugs like Avastin and Cytarabine[169].

Krishnan et al.[170] were among the first to report the efficacy of polymeric NPs in delivering Dexamethasone (Dex) to treat childhood leukemia. They revealed that low doses of Dex would induce cell death and improve survival[170]. Dexamethasone was encapsulated in polymeric NPs composed of an amphiphilic block copolymer of poly(ethylene glycol) (PEG) and poly(ε-caprolactone) (PCL). In mice, these NPs had an antileukemic effect and a diameter of 110 nm. As with free Dex, Dex-NPs induced glucocorticoid phosphorylation and showed cytotoxicity. Dex-NPs improved the quality of life and survival of leukemic mice compared to free drugs. Acharya and Sahoo have suggested applying polymeric nanoparticles to overcome the side effects of high doses of single drugs by administering dual medications at lower doses[171]. They used PLGA NPs to simultaneously deliver two drugs to target sites of leukemia (Bcr–Ab+ oncoprotein) using poly (lactide-co-glycolide) (PLGA) nanoparticles. K562 cell lines were used as model leukemic cells to evaluate NPs' efficacy.

Photodynamic therapy is emerging as an effective non-invasive treatment for cancer. Under UV irradiation, photoexcited nanoparticles and anti-cancer drugs have a synergistic effect on leukemia cell lines. Guo et al.2008 investigated the efficiency of different-sized ZnO nanoparticles on the drug uptake of daunorubicin by K562 and K562/A02 leukemia cells in the presence and absence of UV irradiation[172]. UV irradiation enhanced daunorubicin uptake for both leukemia cells in the presence of ZnO nanoparticles. As reported, the light excited the photosensitizing drug, causing reactive oxygen species to form, responsible for the selective destruction of tumors by the light. CML patients may benefit from stem cell-targeted drug delivery. The persistence of leukemic quiescent stem cells (QSCs), which are capable of causing relapse in patients with CML, makes a cure unlikely. Using synthetic low-density lipoprotein (sLDL) nanoparticles, targeted drug delivery has been shown to overcome sub-therapeutic intracellular drug concentrations in persistent leukemic QSC. Adding anti-cancer agents to sLDL nanoparticles may enhance intracellular drug concentrations in primitive CML cells and aid in their eradication[173] (Figure 3).

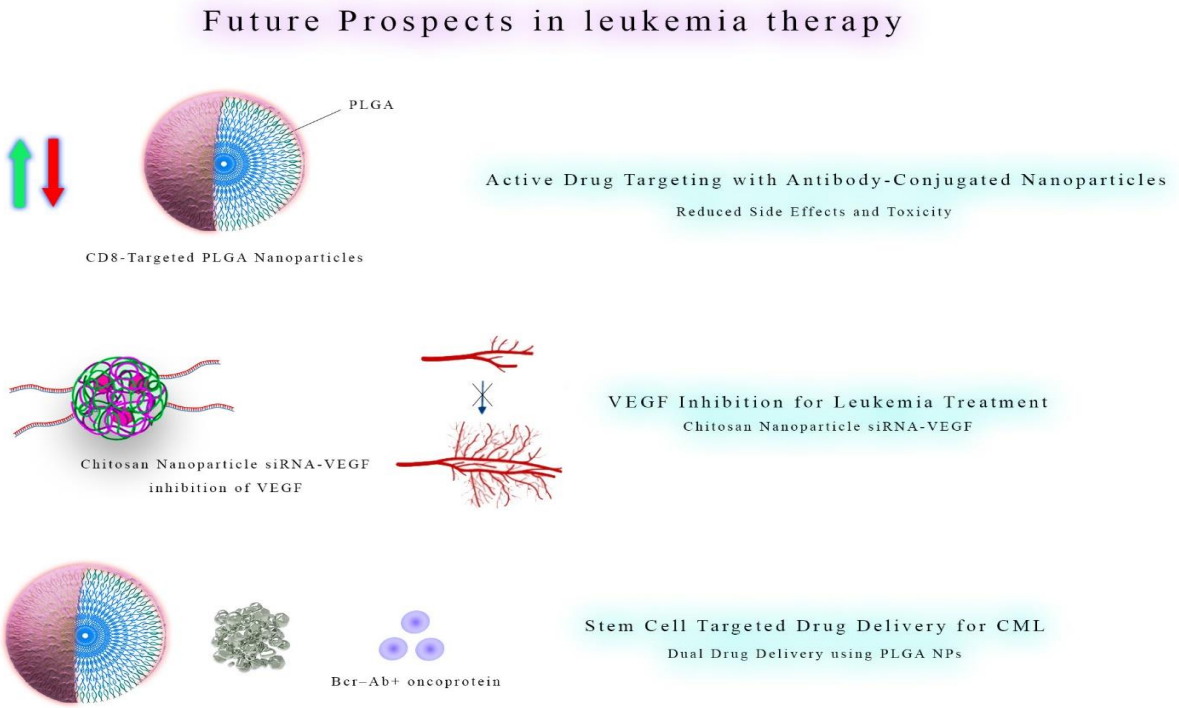

Figure 3. Future prospects in leukemia therapy

In the first panel, PLGA nanoparticles (NPs) conjugated with anti-CD8 antibodies are depicted, showcasing their specific interaction with lymphoblastic leukemia cells expressing human CD8. This targeted approach, illustrated in the second panel, ensures selective drug delivery to leukemia cells, minimizing the impact on healthy tissues and reducing side effects compared to unspecific drug uptake. The third panel focuses on gelatin nanoparticles crosslinked with glutaraldehyde, modified with anti-CD3 antibodies, demonstrating their interaction with T-lymphocytic cells. In the second part of the figure, chitosan nanoparticles carrying siRNA-VEGF are illustrated, emphasizing their targeted inhibition of VEGF in leukemic cells. The combination therapy approach is represented in the last panel, portraying leukemic cells treated with a synergistic combination of siRNA-VEGF, traditional drugs (Avastin, Cytarabine), and chitosan nanoparticles. These strategies showcase promising advancements in active drug targeting for leukemia treatment, offering improved efficacy and reduced side effects.

9. Conclusion

Metal nanoparticles, particularly gold, silver, and iron oxide, promise a breakthrough in cancer treatment. Gold nanoparticles exhibit unique properties for targeted drug delivery and photothermal therapy. Silver nanoparticles, with potent antimicrobial effects, address secondary infections in leukemia patients. Iron oxide nanoparticles in imaging and treatment enable precise drug delivery and magnetic hyperthermia. Other metals like platinum, copper, titanium, and zinc oxide have diverse exploration prospects. The field's promising landscape focuses on precision, reduced systemic toxicity, and novel therapeutic approaches. Despite challenges in biocompatibility, toxicity, and clinical translation, collaborative efforts have been made to address these issues. A potential synergy between metal nanoparticles and existing therapies could revolutionize leukemia treatment, paving the way for improved, targeted, and personalized treatments.

Declarations

Competing interests

The authors declare no conflict of interest.

Authors' contributions

Danial Soltani primarily carried out the conceptualization of the project, while the initial writing and preparation of the original draft involved the collaborative efforts of Ahmad Mir Hosseini, Shiva Dianaty, and Sara Shahhosseini. Subsequently, the project underwent thorough review and editing, with contributions from Reza Biglarifard, Razieh Razmi, and Nima Komeili. The project was self-funded, and Danial Soltani supervised its development. All authors checked and approved the final version of the manuscript for publication in the present journal.

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Ethical considerations

All applicable international, national, and/or institutional guidelines for the care and use of animals were followed.

Availability of data and materials

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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