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REVIEW ARTICLE

Exploring the therapeutic implications of nanoparticles for liquid tumors: A comprehensive review with special emphasis on green synthesis techniques in the context of Dalton's lymphoma

Naveen Kumar[1], Vikram Delu[2], Tarsem Nain[3], Anil Kumar[4], Pooja[5], Arbind Acharya[1]*.

Abstract

Nanoparticles (NPs) have emerged as promising tools for treating and diagnosing various diseases, including cancer, human immunodeficiency virus (HIV), and immune-related diseases. Multiple reviews have been published compiling the effects of NPs on different illnesses. However, a few reviews are available regarding the impact of NPs on liquid tumors. Therefore, this review aims to advance knowledge in this direction by drawing conclusions from research on Dalton's lymphoma (DL), a type of T-cell lymphoma, for the therapeutic implication for liquid tumors. NPs synthesized from both metals (such as silver, gold, copper, and zinc) and nonmetals (such as silica, selenium, polymer, and lipid-based) have been tested for their anticancer efficacy against DL. These NPs reduce the viability of DL cells in a dose-dependent manner by inducing apoptosis. In mice, NPs increase the lifespan, reduce tumor growth, and restore the normal physiology and structure of organs such as the liver, spleen, and kidney. NPs synthesized from plant sources or through some chemical compounds proved effective in reducing the cytotoxicity of NPs. This review will provide basic information on DL and discuss the various types of NPs used against it, their significance for therapeutics of T-cell lymphoma or liquid tumors and conclude with some major findings that can guide future research in this field. By synthesizing the latest research on NPs and DL, this review will serve as a valuable resource for researchers and clinicians alike in their efforts to combat liquid tumors.

Keywords: Mice, Polymers, Lipids, Plants, Cytotoxicity.

[1]Department of Zoology, Institute of Science, Banaras Hindu University, Varanasi, Uttar Pradesh, India.

[2]Department of Zoology, Haryana State Biodiversity Board, Panchkula, Haryana, India.

[3]Department of Genetics, Maharshi Dayanand University (MDU), Rohtak, Haryana, India.

[4]Department of Biotechnology, Chaudhary Devi Lal University, Sirsa, Haryana, India.

[5]Department of Botany, Punjabi University, Patiala, Punjab, India.

***Corresponding Author:** Arbind Acharya, Department of Zoology, Institute of Science, Banaras Hindu University, Varanasi, Uttar Pradesh, India, E-Mail: acharya@bhu.ac.in

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Introduction

Nanoparticles: An emerging nano-therapeutic tool for liquid tumor

The development of nanotechnology, which involves the engineering of functional systems at the molecular scale, has become a crucial advancement in the 21st century. Over the past few decades, a wide range of nano-formulations with sizes ranging from nanometers (10^{-9} m) to micrometers (10^{-6} m) have been designed and tested. These formulations include polymers, micelles, liposomes, nanotubes, and metal nanoparticles (NPs), coupled with various targeting ligands such as small organic molecules, peptides, proteins, antibodies, nucleic acids, therapeutic drugs, and contrast agents (Abdelsattar *et al.,* 2021; Sun *et al.,* 2014). Among these nano-formulations, NPs play a crucial role in the diagnosis and treatment of various diseases, including AIDS (Liu & Chen, 2016), cancer (Goldberg, 2019), infectious diseases (Jackson *et al.,* 2017), diabetes (DiSanto *et al.,* 2015), and autoimmune diseases (Chountoulesi & Demetzos, 2020). Nanotechnology promises to address

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several challenges associated with conventional therapies such as chemotherapy and radiotherapy. These challenges include poor water solubility of many cancer drugs, low therapeutic index, lack of targeted activity, systemic toxicity, and non-specific distribution. In the field of tumor diagnosis, nanotechnology has emerged as a powerful tool for the early detection of tumor biomarkers with enhanced sensitivity and selectivity. Moreover, it enables targeted treatment by delivering therapeutic payloads directly to tumor cells, capitalizing on the spatial pH variations, retention effect, and pathophysiological conditions of the tumor microenvironment. This approach has great potential for overcoming the limitations of traditional therapies and improving patient outcomes. The continued advancement of nanotechnology in the realm of nano-formulations and NPs provides new avenues for the development of innovative diagnostic and therapeutic strategies. By harnessing nanoscale systems' unique properties and capabilities, researchers are paving the way for improved disease management and personalized medicine.

The use of NPs has gained significant attention in the context of liquid tumors, with four principal classes of NPs, namely metal, polymer, silica, and lipid, being predominantly tested. Metal NPs have exhibited robustness in potentiating cancer therapy, demonstrating low toxicity, high surface/volume ratio, good biocompatibility, and biodegradability. Among these, numerous studies have extensively explored magnetic NPs (MNPs) for targeted drug delivery. In the case of acute myeloid leukemia (AML), the combination of MNPs with wogonin, a drug used for AML treatment, has shown promising results. This combination induced apoptosis and arrested leukemia K562/A02 cells in the G0/G1 phase (Peng *et al.,* 2016). Similarly, the loading of another AML drug, cytarabine, onto MNPs demonstrated significantly higher effects compared to cytarabine alone in the HL60 leukemia cell line (Shahabadi *et al.,* 2016). These findings highlight the potential of MNPs as effective vehicles for drug delivery, enhancing the therapeutic efficacy of drugs. In the context of chronic myeloid leukemia (CML), gold NPs (AuNPs) tagged with specific double-stranded DNA (dsDNA) oligonucleotides of BIRC5 and dasatinib (tyrosine kinase inhibitors used in CML) have been employed. This approach involved the release of antisense nucleotides to suppress the overexpressed tumor marker gene BIRC5 in a CML cell line (Gossai *et al.,* 2016). Polymeric NPs formed by the assembly of co-polymers have been extensively utilized for cancer diagnosis, imaging, and therapeutics. In one study, a multistage vector based on polymeric NPs consisting of mPoly ethylene glycol-polylactic acid micelles, encapsulated with degradable porous silicon coated with E-selectin thioaptamer and incorporated with parthenolide (an agent specifically eliminating resistant stem cells of AML), was employed. This vector directed particles towards the bone marrow, specifically recognizing leukemic stem cells through the adhesion molecule E-selectin, eliminating AML burden *in-vivo* (Winkler *et al.,* 2012; Zong *et al.,* 2016). Moreover, co-polymeric NPs have been utilized for the delivery of the anticancer drug doxorubicin (DOX), which was further functionalized with CD-19 antibodies to enhance receptor-mediated endocytosis in CD-19 positive acute lymphocytic leukemia cells. This approach aimed to improve targeted drug delivery (Choudhury *et al.,* 2019). The utilization of various NPs in the treatment of liquid tumors demonstrates the potential of nanotechnology in advancing cancer therapeutics. The precise targeting and delivery capabilities of NPs offer opportunities for enhancing drug efficacy and reducing side effects, providing a promising avenue for the development of novel treatment strategies.

The NPs have demonstrated remarkable attributes such as minimal cytotoxicity to normal cells, reduced systemic toxicity, and higher therapeutic efficacy compared to free DOX (Krishnan *et al.,* 2015). Among the various types of NPs, mesoporous silica NPs (MS-NPs) have gained significant attention due to their unique properties, including tunable pore size and the ability to release drugs in response to pH, temperature, redox reactions, enzymes, or biomolecules (Cheng *et al.,* 2017; Lin *et al.,* 2017). MS-NPs incorporated with DOX and functionalized with rituximab through an avidin-biotin system have demonstrated improved drug release in the acidic environment of endosomes and lysosomes in CD-20 positive B-cell lymphoma, leading to inhibited tumor growth with minimal side effects (Zhou *et al.,* 2017). Another noteworthy class of NPs is lipid NPs (LNPs), encompassing liposomes and micelles, which exhibit the capacity to bind lipophilic or hydrophilic drugs, enhance pharmaceutical stability, and offer diverse applications in drug delivery. LNP-based carriers for DOX have exhibited improved stability and prolonged circulation of the drug in the bloodstream, resulting in increased half-life and significantly reduced side effects compared to conventional DOX chemotherapy (Zhai *et al.,* 2017).

Furthermore, the utilization of nano-constructed poloxamer micelles containing chlorpromazine, a drug employed against multidrug resistance-inducing P-glycoprotein in CML cells, has shown enhanced cytotoxicity and selectivity toward the tumor (Mello *et al.,* 2016). Additionally, the combination of the protease inhibitors carfilzomib and bortezomib with LNPs has been found to promote drug absorption, enhance apoptosis, and reduce systemic toxicity in the treatment of multiple myeloma cells (Ashley *et al.,* 2014). However, despite the immense potential observed *in-vitro* and *in-vivo* mouse models, the limited relevance of these models to human cancer has posed a significant challenge in replicating these effects in clinical trials (Deshantri *et al.,* 2018). Consequently, the actual implementation of NPs has been hindered by difficulties in achieving appropriate pharmacokinetics, reproducible synthesis, and concerns regarding toxicity,

stability, biodegradation, accumulation in healthy organs, and elimination. The broad range of non-ideal effects associated with NPs has restricted their applications at the primary level. Nevertheless, researchers are employing techniques such as capping, green synthesis, and synthesis with other compounds to mitigate these side effects (Hasan, 2015; Jurj *et al.,* 2017). The disparity between the anticipated applications of NPs and the actual products derived from nano formulations prompts us to contemplate whether NPs represent a mere illusion of promise or if the molecular (or atomic) targeting facilitated by nanotechnology truly signifies the future of medicinal biology.

Dalton's Lymphoma - Transplantable T-cell Lymphoma of Spontaneous Origin

Hematological tumors encompass a group of diseases characterized by uncontrolled proliferation of blood-forming cells resulting from mutations and other disruptive events. Lymphoma, a type of hematological tumor related to the immune system, can be classified into two main types: Hodgkin lymphoma and non-Hodgkin Lymphoma (Merryman *et al.,* 2017). Non-Hodgkin lymphoma, which primarily affects B and T-lymphocytes, is the most common subtype. Dalton's lymphoma (DL) is a transplantable T-cell lymphoma that originated spontaneously in the thymus gland of a DBA/2 212 mouse at the National Cancer Institute in Bethesda, Maryland, in 1947 (Gautam & Acharya, 2015). The nomenclature of Dalton's lymphoma derives from Dr. Dalton, who provided it to the first user, and its documentation by author Klein (Klein, 1951). DL is known for its highly aggressive and immunosuppressive nature, inducing rapid and invasive tumor growth. It can be developed in various mouse strains, such as Balb/c (Gautam & Acharya, 2015), AKR (Maurya & Vinayak, 2015), and DBA/2 (Jaylata Devi & Sharan, 2006), with high efficiency. Due to its easy maintenance, reproducibility, and well-characterized properties, DL has become a widely used and intriguing model for clinical model for lymphoma research. DL leads to the impairment of the T-cell population during the early stages of differentiation, resulting in decreased populations of CD4+CD8, CD4-CD8+, and CD4+CD8+ cells, while increasing the population of CD4-CD8- cells (Shanker *et al.,* 2000). It also affects other blood cells, organs, and various body systems to varying degrees. In DL-bearing mice, white blood cell (WBC) counts increase (as DL is a T-cell Lymphoma), while red blood cell (RBC) counts and hemoglobin (Hb) content decreases. Additionally, platelet numbers decrease while neutrophil numbers increase (Rajesh *et al.,* 2011). DL's progressive growth is associated with thymic atrophy, inhibition of thymocyte proliferation, resulting in thymic organization involution, depletion of cell mass, complete disintegration of thymic architecture characterized by massive depletion of cortical regions, and disappearance of corticomedullary junctions (Shanker *et al.,* 2000), which basically replicate the human T-cell lymphoma progression. DL significantly reduces the survival of mice, leading to changes in body weight, altered morphology, increased abdominal volume, lethargy, paleness of eyes, reduced movement, and crucial alterations in immunological parameters (Gautam, 2016). While numerous reviews on the effects of nanoparticles (NPs) on specific diseases have been published over the last two decades, only a few have focused on the impact of NPs on hematological malignancies. In this review, we aim to advance our understanding of the effects of NPs on hematological malignancies by specifically examining the role of NPs in the context of a T-cell lymphoma type, DL (Figure 1 and Table 1).

Metallic Nanoparticles - Key development of Nanoparticles for DL

Silver nanoparticles

Silver nanoparticles (AgNPs) have attracted significant attention from researchers due to their unique physiological characteristics, such as their small size, large surface area, and the ability to undergo surface modification based on their distinct surface chemistry (Calderon-Jimenez *et al.,* 2017; Nowack *et al.,* 2011). Several studies have explored the potential of biologically synthesized AgNPs from various sources, including *Bacillus licheniformis* (Sriram *et al.,* 2010), *Plumbago indica* (Sujin Jeba Kumar *et al.*), *F. religiosa* (Antony *et al.,* 2013), and *Rhizophora apiculata* (Jacob & Shanmugam, 2015), in inducing dose-dependent toxicity to DL cells. Interestingly, these AgNPs demonstrated the ability to increase the survival time of DL-bearing mice by reducing tumor weight and volume and normalizing marker blood parameters, such as RBC, WBC, Hb, and platelet counts. Notably, no hyperactivity or acute or chronic toxicity was observed (Sriram *et al.,* 2010). AgNPs synthesized with *Ficus religiosa* exhibited hepatoprotective effects by restoring liver architecture and reducing the levels of liver enzymes, such as serum glutamate oxalate transaminase (SGOT) and

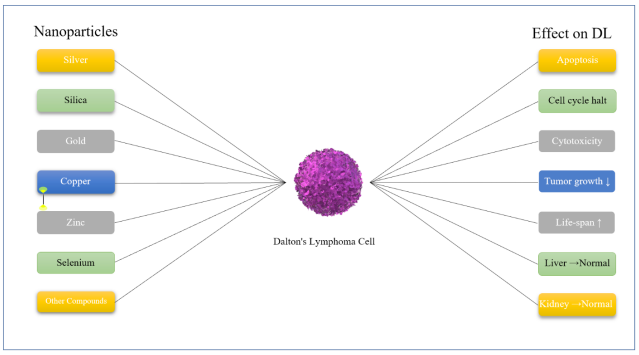

Figure 1: Various types of NPs tested for their anticancer activity against DL. These NPs *in-vitro* induced apoptosis through various pathways halted the cell cycle and showed dose-dependent cytotoxicity on DL cells. In DL-bearing mice these NPs reduced tumor growth, increased life span, and shifted liver and kidney towards normal physiology.

Table 1: Various NPs were synthesized with different plant extracts and compounds of interest

Sr No.	*Type of NPs*	*Synthesized with*	*References*
1.	Silver	*Anabaena doliolum*	Singh G, *et al.,* 2014
		Bacillus licheniformis	Sriram, M. I., *et al.,* 2010
		Commercial 70-nm and 1-nm AgNPs	Onodera, A., *et al.,* 2015
		Doxorubicin and sanazole	Nair GG, *et al.,* 2014
		Ficus religiosa	Antony, J. J., *et al.,* 2013
		Gloriosa superba	M. S., *et al.,* 2017
		Glutathione stabilized nanosilver clusters	Girigoswami A, *et al.,* 2018
		Plumbago indica	Kumar, T. S. J., *et al.,* 2013
		Rhizophora apiculata	Jacob, J. A., & Shanmugam, A. 2015
		Silver-selenium NP synthesized with quercetin and gallic acid	Mittal, A. K., 2014a
		Syzygium cumini	Mittal, A. K., 2014b
2.	Silica	Cadmium selenide	Vibin, M., *et al.,* 2011
		Doxorubicin and ATP	Srivastava, P., *et al.,* 2018b
		Doxorubicin and 5-fluoro-2-deoxyuridine	Srivastava, P., *et al.,* 2020
		Doxorubicin and specific nucleotides	Srivastava, P., *et al.,* 2018a
3.	Gold	*Melia azedarach*	Sukirtha, R., *et al.,* 2012
		Osmium sanctum	Gautam, P. K., *et al.,* 2017
		Poly(ethylene glycol) encapsulating sodium butyrate	Goswami, U., *et al.,* 2018a
		Tamarindus indica	Joseph, M. M., *et al.,* 2014
4.	Copper	Folic acid	Laha, D., *et al.,* 2015
		Transferrin and doxorubicin	Goswami, U., *et al.,* 2018b)
5.	Zinc	*Costus pictus*	Suresh, J., *et al.,* 2018a
		Cyathea nilgiriensis	Suresh, J., *et al.,* 2018b
		Ficus hispida	Kanagamani, K., et a1 2020
		Leucaena leucocephala	Kanagamani, K., *et al.,* 2019
		Turbinaria conoides	Raajshree, R. K., *et al.,* 2018
6.	Selenium	Carboxylic group induced	Kumar, S., et a1 2015
		Carboxylic group induced	Gautam, P. K., *et al.,* 2017
7.	Other compounds	Etoposide loaded with tripalmitin	Reddy, L. H., *et al.,* 2005
		Etoposide with glyceride lipids	Reddy, L. H., *et al.,* 2006
		Hypocrellin B loaded poly(ethylene glycol) modified gelatin NP	Babu, A., *et al.,* 2012
		Poly(ethylene glycol)-modified gelatin and polylactic acid biopolymers loaded with cyclohexane-1,2-diamino hypocrellin B	Babu, A., *et al.,* 2013
		Radiolabeled Poly(lactic co glycolic) acid synthesized with drug etoposide and etoposide	Snehalatha, M., *et al.,* 2013
		Copolymer of doxorubicin-loaded Poly (ε-caprolactone)-b-Poly (N-vinylpyrrolidone)	Hira, S. K., *et al.,* 2014
		Poly(lactic-co-glycolic acid) NP synthesized with tamoxifen	Pandey, S. K., *et al.,* 2016

serum glutamate pyruvate transaminase (SGPT), while increasing alkaline phosphatase (ALP) levels (Antony *et al.,* 2013). Conversely, AgNPs synthesized with *Rhizophora apiculata* showed decreased levels of liver enzymes and increased levels of superoxide dismutase (SOD) and glutathione (GSH) (Jacob & Shanmugam, 2015). In DL, elevated levels of liver enzymes such as SGOT, SGPT, and ALP are commonly observed, along with reduced antioxidant levels, including SOD and GSH (Jacob & Shanmugam, 2015). The reduced antioxidant levels play a significant role in tumoral angiogenesis, which is the formation of new blood vessels from pre-existing ones, while SOD and GSH act as antiangiogenic agents. SOD acts as a crucial defense against oxidative stress by catalyzing the conversion of superoxide to H2O2, and GSH plays essential roles in cellular processes such as differentiation, proliferation, and apoptosis. Furthermore, AgNPs synthesized with *R. apiculata* also exhibited histological restoration of the liver, characterized by a well-defined central vein, cytoplasm containing hepatic cells, and prominent nuclei (Jacob & Shanmugam, 2015). Additionally, AgNPs synthesized with *F. religiosa* demonstrated inhibitory effects on angiogenesis and increased levels of antioxidant enzymes, such as catalase and SOD (Antony *et al.,* 2013).

Apoptosis, a process of programmed cell death, is a common mechanism induced by NPs and most anticancer drugs. It involves various pathways, both mitochondrial-dependent and independent, and encompasses the activation of different proteins and caspases. In the case of DL, AgNPs have shown the ability to induce apoptosis through DNA fragmentation, as observed in studies utilizing AgNPs synthesized from *B. licheniformis* (Sriram *et al.,* 2010), *F. religiosa* (Antony *et al.,* 2013), and *R. apiculata* (Jacob & Shanmugam, 2015). These AgNPs also activate

apoptotic key factors, including caspase-3, 8, 9, 12, p53, and cytochrome C, particularly in the case of AgNPs synthesized with *R. apiculata* (Jacob & Shanmugam, 2015). Another study focused on AgNPs derived from Cyanobacterium *Anabaena doliolum*, which demonstrated tumor growth inhibition through apoptosis induction. The characteristic features of apoptosis were observed, such as contracted cell bodies, condensed chromatin with defined borders, and nuclear fragments containing membrane-bound apoptotic bodies. Moreover, there was an increase in DNA fragmentation, which correlated with the concentration of AgNPs and could be attributed to the production of reactive oxygen species (ROS) (Singh *et al.,* 2014). The synthesis of AgNPs using plant extracts has emerged as a useful approach to mitigate the cytotoxicity associated with bare AgNPs or other NPs. The compounds present in plant extracts, such as proteins, sugars, saccharides, and flavonoids, are believed to play a role in capping these biologically synthesized NPs, thereby reducing their cytotoxic effects (Iravani, 2011) (Zhou *et al.,* 2010). This bio-inspired synthesis method is considered eco-friendly as it eliminates the need for toxic chemicals, high temperatures, or pressure.

In recent years, AgNPs have gained considerable attention as potential agents for cancer therapy due to their unique physicochemical properties. Several studies have investigated the cytotoxic effects of AgNPs on cancer cells and their ability to induce apoptosis and inhibit tumor growth. One such study by Nair and Nair (2014) evaluated the cytotoxicity of Ag-DOX-sanazole (commercial anti-tumor drugs) nanoparticles on cancer cells (Nair & Nair, 2014). The results indicated that the NPs induced apoptosis and reduced the volume and growth of the tumor. Another study by A. K. Mittal *et al.* (2014) synthesized AgNPs capped with quercetin and gallic acid and found that they reduced the viability of DL cells in a dose-dependent manner (Mittal *et al.,* 2014). However, more advanced experiments were lacking. In another study by Onodera *et al.* (2015), commercially bought AgNPs induced the production of apoptosis and ROS (Onodera *et al.,* 2015). Smaller size nanoparticles favored more apoptosis and ROS production, which showed temporal expression and intracellular localization of ROS induced by AgNPs. Additionally, AgNPs protected with different groups like -CH2-, -NH2-, and -CO- of colchicines and colchicine derivatives of *Gloriosa superba* seeds extract were found to be non-cytotoxic to DL cells, while bare AgNPs were toxic, as reported by Devi *et al.* (2017) (Devi *et al.,* 2017). In the succeeding paper of the same group, these AgNPs were found to possess anti-tumor and antioxidant activities with no histopathological variation in tumor-bearing mice (Saradhadevi *et al.,* 2017). Furthermore, a study based on silver nanoclusters (AgNc) was performed by Girigoswami *et al.* (2018), where quantum yield was obtained on DL in different stages of AgNc synthesis to enhance the specificity of killing (Girigoswami *et al.,* 2018). The study found that quantum yield increased initially and then stabilized due to entrapment of AgNc in the macrophage membrane called, macrophages membrane camouflaged silver nanoclusters (Agm). The Agm were found to be more efficient in cell killing than AgNp, which implies that camouflaging of NPs enhanced their activity and stabilized the cell system, reducing side effects.

Overall, AgNPs have the potential to be used in lymphoma therapy. Biologically synthesized AgNPs from various sources have demonstrated dose-dependent toxicity to DL cells, increased survival time of DL-bearing mice, and inhibited angiogenesis. These AgNPs can induce apoptosis through DNA fragmentation, activate apoptotic key factors, and reduce the cytotoxic effects associated with bare AgNPs or other NPs. The bio-inspired synthesis method of AgNPs is considered eco-friendly, eliminating the need for toxic chemicals, high temperatures, or pressure. AgNPs can also exhibit hepatoprotective effects by restoring liver architecture and reducing the levels of liver enzymes, such as SGOT and SGPT, while increasing ALP levels, which are mostly affected during lymphoma progression. Therefore, further research in this area may lead to the development of AgNP-based lymphoma therapeutics.

Gold nanoparticles

Gold nanoparticles (AuNPs) are a promising platform in nanotechnology and medicine due to their simple synthesis, biocompatibility, and versatility in conjugating with bio-molecules via Au-S bond (Cai *et al.,* 2008; Sztandera *et al.,* 2018). These unique properties of AuNPs have led to their successful application in the cytosolic delivery of chemotherapeutic drugs, oligonucleotides, and other compounds (Khan *et al.,* 2014). AuNPs synthesized using green methods such as *Melia azedarach* (Sukirtha *et al.,* 2012), *Tamarindus indica* (Joseph *et al.,* 2014), and *Osmium sanctum* (P. Gautam *et al.,* 2017), have been found to induce apoptosis with typical apoptotic characteristics, and to increase the lifespan of mice through the reduction in tumor volume (Sukirtha, R., *et al.,* 2012, Josephson, M. M., *et al.,* 2014). In our study, we synthesized Au-NPs that arrested the growth of DL cells in G0/G1 cell cycle stage, which is another peculiar feature of apoptosis (P. Gautam *et al.,* 2017). Au-NPs encapsulated with polyethylene glycol and sodium butyrate exhibited no cytotoxicity or adverse effects and reduced the viability of DL cells. In mice, they reduced body weight, increased mean survival time, and reduced WBC and Hb count. Liver marker enzymes SGOT, SGPT, and ALP were reduced, and the liver shifted toward normal hepatocellular ultrastructure, whereas the kidney shifted towards normal renal physiology through the reduction of epithelial desquamation, tubular congestion, and hyperemia (Goswami, Kandimalla, *et al.,* 2018). Surface modifications of Au-NPs with organic compounds such as polyethylene glycol have been shown to prolong circulation

lifetime and enhance the protection of NPs from clearance by the mononuclear phagocyte system.

Overall, AuNPs are a promising platform for lymphoma therapy due to their unique properties, including biocompatibility, easy synthesis, and versatility in conjugation with biomolecules. The use of green methods for synthesizing AuNPs has been found to induce apoptosis in lymphoma cells, increase the lifespan of mice, and reduce tumor volume. In addition, AuNPs encapsulated with polyethylene glycol and sodium butyrate have been shown to reduce the viability of lymphoma cells without causing cytotoxicity or adverse effects. Furthermore, surface modifications of AuNPs with organic compounds such as polyethylene glycol have been found to prolong circulation lifetime and enhance their protection from clearance by the mononuclear phagocyte system. Therefore, the use of AuNPs holds great potential for the treatment of lymphoma.

Copper nanoparticles

Copper nanoparticles (Cu-NPs) have garnered significant attention for their potential in various applications, including electronics, biological, chemical, and organic reactions (Deka *et al.,* 2014; Nasrollahzadeh *et al.,* 2014). Moreover, they have been employed for targeted drug delivery to cancer cells that overexpress certain proteins, such as folate and transferrin receptors. Notably, Cu-NPs synthesized with folic acid (Laha *et al.,* 2015) and with transferrin and DOX (Goswami, Dutta, *et al.,* 2018) have shown promising results in this regard. Specifically, Cu-NPs synthesized with folic acid-induced apoptosis, reduced tumor size, and increased the lifespan of mice with DL. These NPs also increased ROS levels and decreased GSH, while SGOT levels remained unchanged (Laha *et al.,* 2015). Similarly, Cu-transferrin and DOX NPs reduced viable DL cells, tumor volume, and body weight, increasing mice's survival time. Moreover, these NPs normalized abnormal blood parameters, such as DL-induced WBC, RBC, and Hb levels. Additionally, Cu-transferrin and DOX NPs mitigated liver damage, as evidenced by the normalization of SGOT, SGPT, and ALP liver enzymes, and induced normal morphology and physiology in the liver. Likewise, these NPs induced a shift towards normal renal physiology characterized by reduced epithelial desquamation, tubular cast and congestion, medullary part hyperemia, and normal glomerular structures (Goswami, Dutta, *et al.,* 2018). Given that DL growth affects the liver and kidneys significantly, the histological examination of these organs is a valuable tool for evaluating the effects of drugs *in-vivo*.

Cu-NPs can be useful for targeted drug delivery to cancer cells that overexpress certain proteins. These NPs normalized abnormal blood parameters, reduced liver and kidney damage, and induced normal morphology and physiology in these organs. The histological examination of these organs is a valuable tool for evaluating the effects of drugs *in-vivo*. These findings suggest that Cu-NPs have the potential to be used as a therapeutic platform for lymphoma treatment. However, further studies are necessary to determine their safety and efficacy in humans.

Zinc nanoparticles

Zinc oxide nanoparticles (ZnO-NPs) have gained considerable attention from researchers due to their multifunctional spintronic, biocompatible, morphological, and photonic properties ((Hameed *et al.,* 2019). Recently, biological synthesis has been employed for the synthesis of ZnO-NPs (Kanagamani *et al.,* 2021; Kanagamani *et al.,* 2019; Raajshree & Brindha, 2018; Suresh, Pradheesh, Alexramani, & Ig Hong, 2018; Suresh, Pradheesh, Alexramani, Sundrarajan, *et al.,* 2018), Although these studies have demonstrated a dose-dependent decrease in the viability of DL cells, a detailed analysis is still lacking. ZnO-NPs synthesized from *Turbinaria conoides* exhibited enhanced anticancer and antioxidant activities compared to its hydroethanolic extract. The NPs exhibited a protective effect by reducing tumor volume, increasing the lifespan of mice, and restoring altered hematological parameters, liver enzyme activities, and antioxidant status (Raajshree & Brindha, 2018). The detailed study might help decipher the true potential of ZnO-NPs for therapeutic lymphoma.

Non-metallic NPs - A Field of High Significance But Less Explored in DL

Silica nanoparticles

Silica and silicon-based NPs are extensively employed in diagnostics and therapeutics, with solid silica NPs and MS-NPs as the two prominent members of this (Chen *et al.,* 2013). Silica NPs coated with cadmium selenide have been utilized to fluorescently image DL cells, revealing their strong luminescence properties. These NPs may serve as promising molecular imaging tools for studying cellular division, trafficking, and cancer metastasis (Vibin *et al.,* 2011). Additionally, researchers have highlighted the potential of silica NPs as a novel drug delivery system, with various formulations exhibiting remarkable efficacy against DL. For example, nano constructions comprising silica NPs loaded with DOX and an oligonucleotide sequence of telomeres end repeat and telomere substrate primer sequence or DOX and ATP showed dose-dependent inhibition of DL cell proliferation through apoptosis induction (Srivastava, Hira, Sharma, *et al.,* 2018; Srivastava, Hira, Srivastava, *et al.,* 2018). Similarly, MS-NPs nano constructions loaded with DOX and 5-fluoro-2-deoxyuridine effectively inhibited DL cell proliferation through apoptosis induction, and they boosted the growth inhibition potential of dendritic cells towards DL while inducing strong immunity through the induction of killer CD8+ T cells and NK cells (Srivastava *et al.,* 2020). The simultaneous release of two drugs in the same NPs or combination therapy can overcome the drug resistance

problem and lead to a synergistic effect via a complementary mechanism for lymphoma treatment. Furthermore, clinically used chemotherapeutic drugs can be incorporated in a single nano-formulation at a desired ratio, with the advantage of simultaneous release at the target cancer cells.

Selenium nanoparticles

Selenium is a vital trace element that acts as an active component of numerous enzymes, but its NPs are generally considered toxic. To address this issue, various physical, chemical, and biogenic techniques have been devised to decrease their cytotoxicity (Menon *et al.,* 2018). In our study, we developed carboxylic group-induced selenium NP that showed cytotoxicity towards DL cells and reduced their cell viability in a dose-dependent manner. Furthermore, it induced apoptosis characterized by alterations in nuclear morphology, chromatin condensation, and nuclear DNA fragmentation (Kumar *et al.,* 2015). In our most recent study, we found that this NP inhibited tumor cell proliferation and stimulated anti-tumor activities of TAMs (against DL) via ROS generation, increased expression of adhesion and fusion molecules such as CD54 or ICAM-1, and CD47 & CD172α, respectively. Additionally, it enhanced the phagocytic potential of TAMs and formed polykaryons in macrophages (P. K. Gautam *et al.,* 2017).

Polymer and lipids-based nanoparticles

Polymer-based NPs can either be biodegradable or non-biodegradable, with the latter having longer degradation times and lower efficacy. On the other hand, biodegradable polymers poly(ethylene glycol), Poly(lactic-co-glycolic acid), and a copolymer of Poly(ε-caprolactone)-b-Poly(N-vinylpyrrolidone) have been used to synthesize various kinds of biodegradable polymers that effectively reduced the growth of DL cells in a dose-dependent manner. Polymer-based NPs have also been investigated as potential agents for photodynamic therapy (PDT) to treat cancer. For instance, hypocrellin B loaded Poly(ethylene glycol) modified gelatin NPs showed promise as a PDT agent with characteristic optical properties, exhibiting dose-dependent phototoxicity, mitochondrial damage, and photogeneration of ROS upon visible light treatment (Babu *et al.,* 2012). Additionally, biopolymers of Poly(ethylene glycol) modified gelatin and polylactic acid loaded with cyclohexane-1,2-diamino hypocrellin B induced apoptosis via changes in mitochondrial membrane potential, effectively regressing tumors (Babu *et al.,* 2013). Radiolabeled Poly(lactic-co-glycolic acid) NPs synthesized with the anti-tumor etoposide demonstrated potential for prolonged tumor therapy, as the drug was released time-dependent (Snehalatha *et al.,* 2013). Similarly, the copolymer of DOX-loaded Poly(ε-caprolactone)-b-Poly(N-vinylpyrrolidone) effectively prevented growth and metastasis of DL, induced apoptosis, and reduced the number of WBCs, without affecting RBC counts. It also reduced infiltrated metastatic lymphoid cells in the liver, shifted lungs towards normal physiology, and restored capsular architectures of the spleen (Hira *et al.,* 2014). Lastly, Poly(lactic-co-glycolic acid) NPs synthesized with tamoxifen reduced cell viability *in-vivo* and induced apoptosis (Pandey *et al.,* 2016). Combined, polymer-based NPs hold great promise as a novel tool for cancer treatment and warrant further investigation.

Lipid-based NPs (LNPs) are a promising class of pharmaceutical nanocarriers for controlled drug delivery. One remarkable feature of LNPs is their ability to encapsulate a wide range of molecules, from small drugs to large biomolecules, vaccine antigens, and genetic material such as DNA or siRNA (Lingayat *et al.,* 2017; Paliwal *et al.,* 2020). LNPs have been synthesized from tripalmitin and glyceride lipids (mono, di, and triglycerides) and tested against DL (Reddy *et al.,* 2006; Reddy *et al.,* 2005). Etoposide-loaded tripalmitin NPs exhibited anticancer activity against DL, and the most effective administration route was subcutaneous > intraperitoneal > intravenous (Reddy *et al.,* 2005). Glyceride LNPs, including monoglyceride (glycerol monostearate), diglyceride (glycerol distearate), and triglyceride (tripalmitin) loaded with etoposide, induced apoptosis in DL cells and arrested cell cycle in the G2 phase, with the most efficient being etoposide-loaded tripalmitin (Reddy *et al.,* 2006). These results suggest the potential of LNPs for targeted drug delivery in cancer therapy.

In a nutshell, it can be concluded that nanoparticle-based therapies, specifically polymer-based and lipid-based nanoparticles, show promise as effective tools for the treatment of lymphoma. Biodegradable polymers such as Poly(ethylene glycol), Poly(lactic-co-glycolic acid), and Poly(ε-caprolactone)-b-Poly(N-vinylpyrrolidone) have shown efficacy in reducing the growth of DL cells, inducing apoptosis, and preventing metastasis, which could be beneficial in lymphoma therapy. Polymer-based NPs have also shown potential as agents for photodynamic therapy. Similarly, lipid-based NPs have been found to effectively encapsulate a wide range of molecules and exhibit anticancer activity against DL cells. Overall, these findings suggest that these NPs have the potential to be targeted and effective tools for the treatment of lymphoma, and further investigation is warranted.

Future Prospective of Nanoparticles for Liquid Tumors

The rapid advancement in nanotechnology over the past two decades has brought forth a plethora of nano-formulations and synthesis methods for the development of NPs with controlled and optimized structure, shape, size, characteristics, and ligand conjugation to target hematological tumors. NPs offer a broad reactivity, lower cytotoxicity, biocompatibility, target specificity, and bioavailability through innovative and novel approaches

that hold promise for alternatives to traditional liquid cancer treatments like chemotherapy. Specific and targeted drug delivery-based therapies such as polymer and LNPs are crucial for the future of hematological malignancies. Developing a specific drug delivery system for both liquid and solid tumors using NPs requires adhering to three "SSS" golden rules: (i) Specific and selective ligands to target cancer-specific markers or cell surface receptors/ biomolecules, which are highly overexpressed in particular cancers; (ii) Stimuli-responsive drug delivery system that unloads drugs triggered by specific conditions in the tumor microenvironment or cell-specific conditions such as pH, redox potential, or enzymatic activity; (iii) Smarter detectable tracer molecules that allow for direct or easy visualization of drug delivery to the target site. These golden rules will facilitate optimized drug delivery, minimize side effects on normal cells, and aid in developing and formulating NPs based on drugs.

Despite the promise of NPs for drug delivery, several inconsistencies and questions regarding their physical, chemical, and biological activity dampen their potential. Inconsistent synthesis methods, experimental procedures, and applied doses can cause replication problems and produce different behaviors *in-vitro* and *in-vivo*. Conjugation of drugs or active compounds to NPs can also lead to decreased activity and difficulties with kinetics stability and release, requiring comprehensive testing and optimization. Additionally, the challenge of developing non-toxic and controlled methods of NPs synthesis is daunting, as even slight changes in physicochemical properties can drastically affect their biological activity. Thorough testing of tagging compounds for possible systemic toxicity and side effects in living beings is essential. To overcome these problems, models such as DL can be used to understand and address inconsistencies and replication issues. Green synthesis, polymer and LNPs offer efficient and targeted drug delivery with less toxicity to other cells, making them an attractive option for cancer treatment. However, the development of antileukemic drug formulations, targeted gene silencing, and targeted delivery must be a prime focus. NPs can also be used for diagnosis, as target-specific assay kits based on NPs can offer higher sensitivity and specificity than presently available kits. The ability of NPs for easy conjugation can also be utilized to develop a drug for simultaneous diagnosis and treatment. The use of xenograft models can mitigate the non-relevancy and failure to replicate mice model results in the complex human microenvironment, ultimately leading to clinical trials and achieving the ultimate goal of NPs.

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