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Nanoparticulate-based formulations conquering the barriers of Retinoblastoma

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Abstract

In the last decade, site-directed administration and increased bioavailability have led to significant advances in cancer delivery technologies with nano-deliverable technologies (NDPs). Gold nanoparticles, liposomes, Dendrimers (Biodegradable Polyesters), and Mesoporous Silica are some of the most widely used nanoparticle systems in the field of cancer treatment. Retinoblastoma (RB) is a rapidly developing childhood eye cancer. Nanoparticle-based systems that have been mainly investigated for RB therapy have displayed improved drug delivery to the most restricted posterior segment of the eyes and have increased the intra-vitreal half-life of the chemotherapy agents highlighting its potential in the treatment of this form of cancer. It highlights the work that has been done to develop Nano-Dimensional Systems for RB treatment. This paper focuses on the current and emerging therapy options for diagnosing and treating the disease. It also describes how anticancer and imaging drugs can be actively directed to tumor cells with ligand-convulsant and smart nanoparticle applications. Finally, this paper discusses the opportunities and challenges in bringing this nano-carrier to clinical use for the treatment of RB. This paper may provide new perspectives for formulation researchers to study to support the development of safer and more effective medications for children with retinoblastoma.

Keywords: Retinoblastoma, Nanoparticles, Cancer, Nano dimensional system, liposomes, dendrimers, eye cancer

1. Introduction

One kind of pediatric eye cancer that is commonly found is called retinoblastoma (RB) [1]. At a frequency of one in fifteen thousand, it is most common among children under five years old [2]. Even though there is a high survival rate of approximately 95% for this type of cancer, if treatment is not received, the disease can advance and cause serious visual impairments as well as death [3]. Additionally, there is a discrepancy in patient survival rates between continents. With a mortality rate of roughly 4-5 percent, patient survival and cure rates are said to be exceptionally high in the United States. On the other hand, the mortality rate in Asian and African nations ranges from 39 to 70% [4]. The main causes of this significant difference in patient survival rates are inadequate preventative measures and a delayed diagnosis of this kind of cancer [5]. In approximately 90% of RB cases in underdeveloped nations, a delayed diagnosis carries a poor prognosis for patient survival. As a result, cancer advances quickly into the metastatic and fatal stages [6]. To enhance patient survival over the long term after detection, prompt medical intervention, including a multidisciplinary team made up of oncologists, ophthalmologists, radiologists, and geneticists with the proper chemotherapy, radiation, and surgical procedures, is necessary [7].

Histologically speaking, the development of RB has been associated with the proliferation of undeveloped retinal cells and the eventual removal of the retina and other intra-ocular tissues. RB is characterized by a rapid rate of mitosis and many areas of necrosis and dystrophic calcification [8]. Alfred Knudson proposed the "two-hit" hypothesis in 1971, which states that mutations can cause RB in particular cells within the retina, altering the cell cycle in a way that makes it difficult for the cell to enter the S phase or in the germinal stage affecting all retinal cells.

RB may occur in families or develop randomly. One notable characteristic of the hereditary RB is that both mutations occur before development; as a result, cancer tends to develop into a bilateral RB at a younger age [9], Figure 1. The somatic mutations are frequent in the sporadic form of RB, and both mutations occur in a single retinal cell following fertilization. Because of this, this kind of cancer frequently strikes later in life and is not typically passed on to the offspring [10].

In terms of genetics, RB is defined by either the deletion or incorrect expression of the tumor suppressor gene RB1, which is located at chromosome 13q14.2 [11]. Only when both RB1 gene copies function abnormally or are completely deleted does RB occur [12]. These occurrences take place either before or during the fertilization phase, which results in the

creation of a bilateral RB that is inheritable [13]. However, many investigations have shown that not all cases of bilateral RB are inherited. Bilateral RB can also result from de novo mutations during spermatogenesis [14]. When one retinal cell experiences a mutation after fertilization, it results in unilateral RB in the sporadic form of the condition [15]. It has been determined that 15% of cases of unilateral RB may result from inherited germinal mutations, despite the previous belief that all cases of unilateral RB are caused by somatic mutations [16]. The color changes associated with strabismus and pupil red reflex are being used as indicators for the possibility of the beginning of RB [17]. Further methods for detecting the existence of a white, creamy mass and intra- and extraocular extensions that are frequently linked to RB include fundoscopy, eye ultrasonography, and magnetic resonance imaging (MRI) [18]. Early diagnosis and awareness of the danger associated with producing offspring with inherited RB can be achieved by genetic counseling and the identification of prone family members [19].

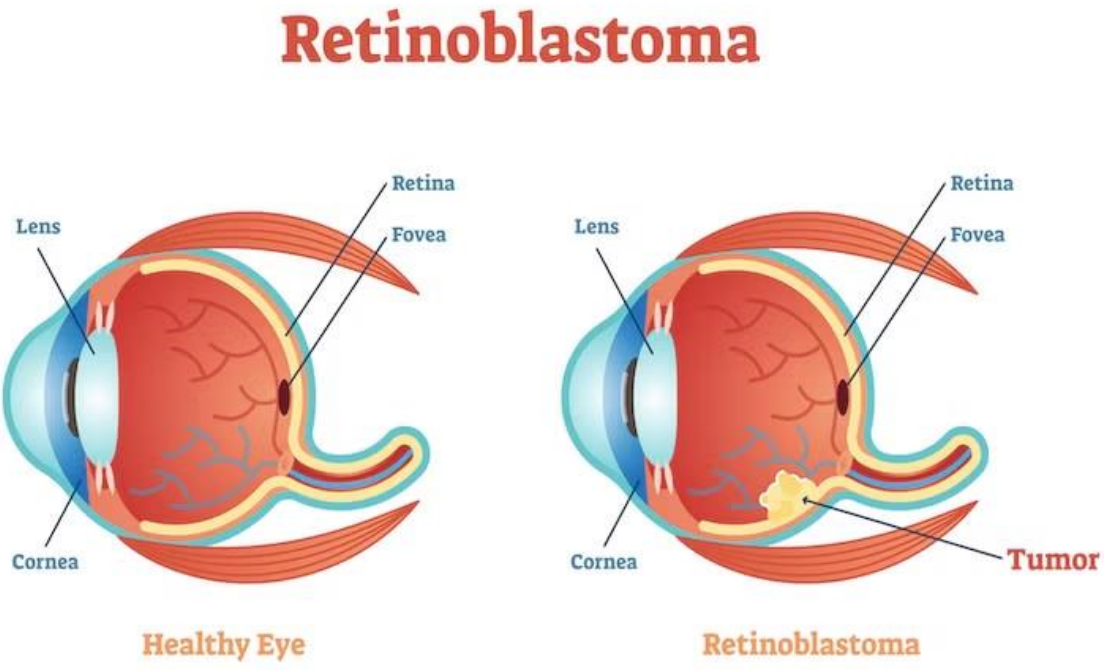

Figure 1: Illustration showing healthy eye and retinoblastoma

2. Current treatment options for retinoblastoma

Depending on the stage, retinoblastoma can be treated by systemic or local chemotherapy, cryotherapy, radiation therapy, laser therapy (thermotherapy or photocoagulation), or a combination of these.

Radiotherapy: Two forms of radiation therapy are utilized for retinoblastoma: external beam radiation therapy (EBRT) and brachytherapy, which is also known as plaque radiotherapy.

While both treatments use high-energy radiation to destroy tumor cells, the radiation source's placement varies. The radiation used in brachytherapy is applied to the sclera, or outer layer of the eye, using a capsule that contains a radioactive substance. For small-to-medium-sized tumors that are more than 3 mm from the optic disc, brachytherapy is employed. The radiation used in external beam radiotherapy comes from an external source. Tumors near the optic nerve and retinoblastoma that are not responding to conventional therapies can also be treated with EBRT. Due to the hazards connected with it, such as second cancer risk in patients with heritable retinoblastoma, secondary sarcoma, retinopathy, midface hypoplasia, and cataracts, it is only performed when necessary [20, 21]. Because of difficulties brought on by radiation, enucleation will still be required after radiation therapy.

Cryotherapy: Through the use of a probe positioned on the sclera, liquid nitrogen is delivered to nearby tumors during cryotherapy, freezing and killing the cells [22]. Small tumors in the anterior region of the eye are treated with it. Retinal detachment, vitreoretinopathy, and chorioretinal atrophy are among the potential side effects of cryotherapy [23].

Laser therapy: Thermal therapy or photocoagulation can be used in laser therapy for retinoblastoma. During photocoagulation, the blood vessels surrounding the tumor are heated and destroyed by a laser beam. Small tumors in the posterior eye that are not near the optic disc or fovea respond well to this treatment. Retinal detachment, traction, and vascular occlusions are among the side effects of this treatment [24, 25]. Transpupillary thermal therapy, or thermotherapy, kills cancer cells by shining infrared light on the tumor. This course of treatment is limited to tiny tumors, including those that are close to the optic disc or fovea. For big tumors, it can be used in conjunction with radiation therapy or chemotherapy [26]. Iris atrophy, retinal fibrosis, and cataracts are among the side effects of thermotherapy.

Chemotherapy: Cytotoxic drugs are used in chemotherapy to destroy cancer cells. Chemotherapeutic agents can be given locally (intra-arterial or intravitreal) or systemically (intravenous). Carboplatin, cisplatin, etoposide, vincristine, topotecan, and melphalan are anticancer medications that are often used. The use of two or three cancer-fighting drugs in combination with systemic chemotherapy, often known as "chemo reduction," reduces tumor size and boosts the efficacy of focused therapies such as laser treatment, brachytherapy, or cryotherapy. Even after surgery, when cancer has progressed to other body parts and the eye, adjuvant and intrathecal chemotherapy are utilized.

On the other hand, systemic chemotherapy is linked to serious adverse effects such as kidney, liver, and ear damage, temporary neutropenia, and subsequent malignancy [27, 28]. Their non-specific absorption and dispersion throughout the body are the primary causes of these effects. Consolidation with focused therapy typically occurs after systemic chemotherapy.

A new strategy called local chemotherapy was created to get around the problems with systemic chemotherapy. Anticancer medications are injected directly into the vitreous cavity of the eye or through the ophthalmic artery, boosting the concentration of the drug at the target size and minimizing systemic adverse effects. Intravitreal chemotherapy is an effective way to control vitreous seeding, which is a sign of advanced malignancy. Patients with advanced retinoblastoma have greatly benefited from this local treatment in terms of saving their eyes [29, 30]. Retinal pigment epithelial changes, pulmonary toxicity, arrhythmias, vitreous hemorrhage, and retinal vasculitis have all been linked to local treatment with melphalan. [32, 31] Local chemotherapy is not available to patients in developing nations, is costly, and needs highly qualified workers. Thus, in those nations, surgery continues to be the primary treatment for advanced retinoblastoma.

Enucleation: The quickest and least expensive treatment is enucleation, which involves surgically removing the eye. It also has no systemic complications and lowers mortality [33]. Due to its non-conservative nature, the eye and facial abnormalities are permanently lost. As a result, it is still only used for well-advanced retinoblastoma. The available and developing treatments for retinoblastoma are summarized.

3. Emerging treatment options for targeting retinoblastoma

The goal of emerging therapy alternatives is to overcome the limitations of existing treatment regimens through focused study. To encourage dedicated research efforts in the creation of innovative, new therapeutic compounds or delivery methods that would enhance clinical efficacy and drastically lower toxicity, hence enhancing the chances of survival for retinoblastoma, it is pertinent to review the current treatment options for retinoblastoma and their shortcomings.

New or repositioned drugs: Conventional drugs like melphalan and etoposide have side effects that include organ damage and an increased chance of developing secondary tumors. The high rate of side effects associated with these medications has made it more and more necessary to look for new or repositioned medications that have intrinsically selective effects on the tumor cells in the ocular tissue. The current methods for finding new medications and

repurposing existing ones to produce ocular-specific innovative therapeutic candidates for the treatment of retinoblastoma. Using the latest innovations, drug discovery is achieved by identifying irregular pathways in the retinoblastoma growth process. Using outdated drugs for novel therapeutic indications is known as drug repositioning, and it is a quicker and less expensive strategy [34]. To this end, cardenolides were found to be effective against retinoblastoma in high throughput screening studies. A patient in this study was claimed to have been cured of retinoblastoma following digoxin delivery by ophthalmic artery chemosurgery; nevertheless, a cataract formed as a result, most likely due to the method of administration. Digoxin is a repurposed medication; therefore, reducing its ocular and cardiac toxicity may be possible by optimizing the route of delivery. Finding the targets of tumors and creating direct treatments is a further strategy. To achieve this, inhibitors of the proteasome, NF-KB, histone deacetylase, kinesin spindle protein, STAT 3, survivin, Bcl-2 proteins, and bromodomain and extra-motif proteins (BET) have been identified and are in the early phases of pharmacological development [35]. The results of transcriptomic and genomic studies of retinoblastoma tumors have demonstrated the dysregulation of BRCA1 and RAD51, two DNA repair proteins. Combining the chemotherapeutic medication topotecan with a specific RAD51 inhibitor showed a synergistic antitumor activity [36]. The MDM2/MDM4-p53 pathway is the best-studied dysregulated route in retinoblastoma [37]. The overexpression of MDM2-p-53 and its homolog MDM4-p53 inhibits transcription and causes P53 protein breakdown in retinoblastoma [38]. The use of MDM2/MDM4 inhibitors is the subject of ongoing phase I and II clinical investigations. A newer approach is to target HDM2, another p53-negative regulator that has been demonstrated to induce retinoblastoma cell death [39]. Other possibilities for drug discovery include the BET inhibitor, the repurposing of calcium and potassium channel blockers, and the MYC/MAX signaling, which has driven the hunt for MYC/MAX inhibitors [40].

Targeted drug delivery: Targeted delivery of drugs has become important due to the systemic and local toxicity associated with the use of conventional chemotherapeutic medicines in the treatment of retinoblastoma. Chemotherapeutic drugs with targeted drug delivery concentrate the drug at the intended site of action, minimizing side effects and increasing therapy efficacy and prognosis. In addition, it is critical to evenly disperse chemotherapeutic agents precisely because the posterior portion of the eye has a low drug bioavailability, which increases the possibility of treatment failure, among other problems [41]. Drug delivery targeted at retinoblastoma cells is made possible by the activation of certain receptors in these cells that

show affinity for a variety of ligands, including hyaluronic acid, galactose, mannose, and folic acid [42].

Immunotherapy: Treating retinoblastoma with immunotherapy has great potential for success because of its precision and targeting. Recently developed CAR T cells target the highly expressed neural cell adhesion glycoprotein CD171 and ganglioside GD2 on the surface of retinoblastoma cells. It has been shown that these CAR T cells were cytotoxic when given to a panel of retinoblastoma cells [43]. The anti-GD2 CAR T cell-based formulations that were created for intravitreal administration in the treatment of retinoblastoma subsequently showed no ocular toxicity or recurrence and provided a full antitumor response [44].

Novel drug delivery systems: New drug delivery methods for retinoblastoma cells have been studied, including hydrogel, liposome, polymeric, lipid, and inorganic nanoparticles. [46, 45] They have shown great potential for continuous, targeted, and controlled administration with a few side effects. These systems are used as carriers for genes and imaging agents in addition to cytotoxic drugs. In addition, they can have their surfaces transformed or functionalized to enhance their pharmacokinetic qualities.

4. Role of nanotechnology in the diagnosis of retinoblastoma

As with other cancers, there is a need to manage the risk of intraocular cancer issues and the possibility of metastases [47]. Due to its proximity to essential ocular tissues, early identification of intraocular cancer is critical for preserving vision [48]. Based on the typical age of occurrence, two forms of intraocular tumors can be categorized: adult ocular melanoma and childhood RB [49]. RB, a condition that is frequently hereditary, affects children under five years old and is brought on by the RB gene becoming downregulated. The number of cases of this particular form of intraocular cancer is higher in poorer nations. The limitations on cell cycle regulation that cause uncontrolled cell growth are removed when this gene is silenced [50, 51]. In severe cases, ocular inflammation may result from extraocular infection of the tumor. RB has the potential to spread to the brain, spinal cord, and pleural cavity. It is also possible for the choroid vasculature to penetrate and distribute itself to the bone and stem cells [52].

An ophthalmologist is frequently able to diagnose RB after evaluating and imaging the patient's eye. The diagnosis of a large tumor with retinal and vitreous space lesions, usually white to cream in color, can be seen by fundoscopy. Since CT scans are not suggested for young children, ultrasonography is used to evaluate and identify intraocular malignancies [53, 54].

Additionally, magnetic resonance imaging (MRI) of the brain and orbit is used to study the tumor's extraocular extension [55]. Considering the wide variety of ophthalmic imaging techniques, conventional optical and ultrasonography imaging is not useful in detecting the early abnormalities of ocular disorders until morphological changes become noticeable. On the other side, some diagnostic techniques have been developed to enhance health outcomes. However, there are limitations and drawbacks when using the current techniques [56]. Also, many recent studies have identified new RB biomarkers that may be applied as diagnostic prognostic factors, help in the understanding of RB causes, and provide information about possible therapies and diagnostic strategies [57]. The most important aspect of an effective treatment plan for RB is early identification [58]. New molecular contrast agents and nanomaterials are made possible by nanotechnology, allowing for faster and more accurate initial cancer patient detection as well as ongoing therapy monitoring [59-63]. Many types of nanoplatforms have recently been developed to improve the image quality of traditional imaging methods [64-67]. In the middle of this development, little research has been done to improve the efficiency of traditional ocular imaging methods using nanoplatforms, including MRI, ultrasound imaging, and optical coherence tomography [68].

The use of quantum dots (QDs) in ocular imaging has been studied. They can facilitate multimodal detection and have great optical durability [69,70]. Cultured human corneal endothelial cells (cHCECs) are injected into the anterior chamber as a recently developed therapeutic therapy for corneal endothelium failure. Toda et al. studied cultured human corneal endothelial cells (cHCECs) marked by semiconductor QDs to monitor injected cHCECs. To look into the kinetics and aggregation of QD-labeled injected cHCECs, they examined the effectiveness of in vivo fluorescence imaging in a corneal endothelial dysfunction mouse model [71]. In this study, QD labeling did not cause any changes in the morphology of the cHCECs or the expression of cHCECs' functional markers. Measurements were made of the injected cHCECs QDs. The outer layer of the cryogenically damaged corneal endothelium in mice eyes showed definite preservation of cHCECs QDs from 3 to 48 hours after cell injection, but this was not the case in the healthy, undamaged control eyes.

If the toxicity of the dots is taken into consideration, QDs might be ideal contrast agents. AuNPs have been suggested by several studies as a substitute. In addition to QDs, AuNPs can function as ideal contrast agents for imaging; in recent years, several scientists have employed AuNPs to image ocular cancers [72]. Cruz-Alonso et al., for example, provided an immunohistochemical method for illustrating metallothionein 1/2 (MT 1/2) and metallothionein 3 (MT3) distribution in human ocular tissue [73]. ICP-MS can be coupled with

Au nanocluster (AuNC)-connected antibodies, which are used as markers in this technology. Carbodiimide coupling was used to create water-soluble fluorescent AuNCs with an average size of 2.7 nm, which were later covalently attached to antibodies. Subsequently, the modified AuNCs' 1 surfaces were blocked with hydroxylamine to prevent unwanted interaction with biological tissue. The antigens (MT 1/2 and MT 3) were detected by LA-ICP-MS using a laser point size of only 4 µm since each nanocluster's more than 500 Au atoms increased the signal. The image patterns detected in the retina in this study agreed well with those produced by the traditional immunohistochemistry of fluorescence. Lapierre-Landry et al. studied endogenous (melanin) and exogenous (Au nanorods) absorbers in the eye using in vivo photothermal optical coherence tomography (PT-OCT) for the first time in a different study [74]. OCT is now considered to be treatment quality in retinal imaging. OCT lacks the specificity of contrasting chemicals that could be employed for in vivo molecular imaging, but it makes noninvasive tissue architecture mapping easy. A useful method based on OCT that was created in a sample to determine the absorbers is known as PT-OCT. The photothermal signal in the retina was separated from the melanin in mice that were pigmented and albino. After systemic injection of Au nanorods to explore their passive aggregation in the retina, visual complaints were also observed in a pigmented mouse model with laser-induced choroidal neovascularization lesions. According to the current study, it is possible to identify the distribution of endogenous and exogenous absorbers in mouse eyes by combining the PT-OCT method with Au nanorods. Kim et al. showed the therapeutic application of fucoidan-coated Au NPs and those encapsulated by doxorubicin (DOX) for chemotherapy and dual photothermal treatment (PTT) of ocular malignancies in vivo and in vitro [73]. Fucoidan produced from marine sources is used as a capping agent to increase the photostability of AuNPs, and DOX was added to activate an anticancer chemotherapeutic medication. High tumor cell cytotoxicity and good light absorption for in vitro temperature rises were shown by the produced DOX-fucoidan@AuNPs. PTT-assisted NPs caused the total and nonrecurrent elimination of eye tumors for 14 days following intratumoral injection of DOX-fucoidan@AuNPs into rabbit eye tumors. The photoacoustic image contrast from the tumor tissues was significantly increased as a result of the injected NPs' responsive light absorption. It's interesting to note that using fucoidan produced from marine sources along with AuNPs can enhance their capacity for more effective photothermal therapy. Additionally, Altundal et al. studied the dosimetric effectiveness of using carboplatin loaded AuNPs or AuNPs with carboplatin to improve irradiation efficacy for RB during kV energy external and internal beam radiotherapy and ocular cancers (choroidal melanoma) [74]. The data suggest that combining radiation therapy for eye cancer with AuNPs

or AuNPs laden with carboplatin and administered with kV energy photon rays could result in large dose improvements. In the kV energy range, radiation sources produce more dosage improvements than an external ray.

However, one advantage of the external beam is that it is noninvasive. Moradi et al. used a rabbit model to assess the effectiveness of brachytherapy with ultrasonic hyperthermia techniques in the presence of AuNPs on ocular RB cancers [75]. Day zero and the end of the third week were used to evaluate the tumor area using a B-mode ultrasound imaging technique. A histological diagnostic of the tumor necrosis was made on the groups by study. Comparing the relative tumor area changes of the combination group to the other trial groups, there was a visible difference. Live RB cell necrosis was verified by the histology study's results.

Further, the AuNPs showed excellent proficiency in a variety of imaging modalities, including ultrasounds. As a result, AuNPs might be an ideal replacement for quantum dots. These days, carbon nanomaterials are attracting a lot of attention because of their structural variations and a wide variety of electrical and chemical properties based on functional principles [76]. Due to the flexibility and responsiveness that electrochemical techniques offer when designing a sensor, researchers have focused on electroanalysis employing carbon materials for biomolecules [77]. For example, Goto et al. reported the use of a nanocarbon film electrode for the direct electrochemical detection of DNA methylation in relatively long sequences. The film has a mixed bond structure of nanocrystalline sp(2) and sp(3) and was created by the electron cyclotron resonance sputtering technique [78]. Without using a bisulfite reaction or labeling, their methylation identification method calculated the differences between the 5-methylcytosine and cytosine oxidation currents. Measuring methylated 5'-cytosine-phosphoguanosine (CpG) repeat oligonucleotides using different methylation ratios was made possible by the sensor and the film electrode under ideal conditions. Although carbon nanostructures are highly effective and have low toxicity, there are just a few papers available for RB diagnosis. MRI contrast-enhancing magnetic nanoparticles (NPs) have proven successful in an in vitro environment until now [79].

According to studies, cross-linked therapeutic factors' half-lives can be extended by human serum albumin-coated iron oxide (IO) NPs (HSA and IO/HSA NPs), indicating the possibility of controlled therapeutic delivery using them. Tzameret al. evaluated the long-term safety of IO/HSA NP delivery into the suprachoroid of a rat retinal model as well as in vivo monitoring by MRI to do additional research [80]. In a different work, Jaidev et al. produced fluorescent iron oxide nanoparticles and evaluated their efficacy against RB cell imaging [81]. Oleic acid

was used to create and maintain the iron oxide nanoparticles. Sulforhodamine B was adsorbed onto albumin over iron oxide nanoparticles coated in oleic acid.

The nanomaterials' strong negative contrast to cancer and normal cells in MRI images suggests their bioavailability without causing damage. Iron oxide (IO) NPs have been the most often utilized NPs in MRIs up to this point. Some of the stability and toxicity problems may be reduced by the coating procedure. The importance of using nanotechnological approaches in cancer imaging for eye diagnosis cannot be overstated. Multifunctional nanostructures allow simultaneous monitoring of the intraocular tumor responses to several localized chemotherapies.

A multifunctional nanostructure for imaging-driven multimodal low-intensity focused ultrasound (LIFU)/immune synergistic RB treatment was reported by Wang et al. Fe_3O_4 NPs (AuNCs-Fe_3O_4) were connected to magnetic hollow 5 mesoporous Gold nanocages (AuNCs) to encapsulate perfluoro pentane (PFP) and muramyl dipeptide (MDP). Multifunctional nanoparticles with magnetic properties (NPs) improved in vivo and in vitro photoacoustic, ultrasonic, and magnetic resonance imaging (MRI), which was advantageous for therapeutic and efficacious imaging. When the NPs were exposed to LIFU radiation after accumulating in tumors using a magnetic field, MDP was discharged. AuNCs-Fe3O4/MDP/PFP increased the curative efficacy of LIFU and directly caused tumor apoptosis or necrosis, while MDP encouraged dendritic cell (DC) maturation and activation, allowing DCs to recognize and eradicate tumor cells. The multifunctional AuNC-Fe_3O_4/MDP/PFP NPs demonstrated tremendous promise for immunological synergistic therapy and multimodal imaging-guided LIFU/RB by enhancing magnetic resonance imaging, photoacoustic imaging, and ultrasound imaging while also preventing tumor growth. We think that the most effective way to diagnose RB efficiently is to combine several NPs with varying abilities.

Nanoparticles

As was previously established, RB is the most prevalent eye cancer in children and is brought on by mutations in the tumor-suppressor gene RB1 [82]. Lower socioeconomic position is the reason for a delayed diagnosis, and RB survival rates have declined in developing nations [83]. Mutations in suppressor genes activate proliferation and cancer [84]. The only method of treating RB is enucleation [85]. While external beam radiation therapy is being developed, neutropenia, thrombocytopenia, renal toxicity, systemic toxicity, and hepatotoxicity are linked with all forms of radiation and chemotherapy [86,87]. So, due to protective barriers in the ocular tissues, medication administration in the eye is difficult. In addition, drug delivery

through different nanoformulations is effective enough to get around these restrictions [88,89]. Metallic NPs, lipid-based NPs, and multifunctionalized NPs are the most often used and effective NPs for treating RB [90,91]. Synthesized nanoparticles, on the other hand, can encapsulate the therapeutic moiety and lengthen the retention period [92]. Polymeric NPs exhibit biodegradability and can be safely and efficiently injected intravitreally into rabbit brain tissue.

Multi-functionalized nanocarrier

The synthesis of multi-functionalized NPs involves attaching specific ligands to the NPs to target tissues that exhibit high levels of overexpression in particular diseases. These NPs proved an important discovery in both malignant cancers and a wide range of infectious disorders. Multiple ligands are attached to the nanocarrier system in infectious disorders, making it multifunctional to target intracellular pathogens [93,94].

Surface-modified melphalan nanoparticles for the intravitreal chemotherapy of RB

A two-step formulation was created using the single and double-step emulsion approach by Lee B. Sims et al. [95]. Using the emulsion solvent evaporation approach, Poly-D,L-lactic-co-glycolic acid (PLGA) NPs were first created by encapsulating the fluorescent dye coumarin 6 (C6), which allowed for visibility by fluorescence microscopy. The development of coumarin encapsulation involved creating a single emulsion process based on oil-in-water (o/w). The emulsion was made in batches (100–200 mg) using carboxyl-terminated PLGA. After that, C6 was immersed in dichloromethane (DCM) for the duration of the night, and a tiny amount of PLGA was added at the end. After the final formulation of PLGA/C6/DCM was added, it was agitated, sonicated, and allowed the solvent to evaporate for three hours in a 5% polyvinyl alcohol (PVA) solution. The medication was mixed into melphalan PLGA NPs using the double-emulsion method as the second phase in the formulation process. Melphalan spills during the fabrication process were minimized by using the double-emulsion procedure. Melphalan was dissolved in the EDTA buffer, and PLGA was dissolved in DCM for an entire night to create the double-emulsion procedure. After dissolving melphalan/EDTA in the prepared PLGA/DCM combination, the mixture was continuously stirred. After adding the combination in small increments to the 5% PVA solution, the resulting PLGA/DCM/melphalan/PVA solution was vortexed and sonicated to create the final mixed conjugate. The final nanoparticles produced were hardened to stop melphalan from leaking out of NPs while they were being synthesized.

Galactose functionalized nanocarriers

There is a great need for the sugar moieties ligand-based mechanistic approach for more effective and focused therapy against RB. Compared to healthy cells, RB exhibits a significant overexpression of sugar moieties in the form of lectins. Therefore, overexpressed lectins can be targeted to produce effective outcomes. Through the use of carbodiimide chemistry, Godse et al. established a unique sugar receptor-targeted delivery method in this study that allows for the safe and targeted distribution of etoposide (ETP) by conjugating a galactose carboxyl group with amino groups of chitosan (GC) [96]. ETP was first inserted into poly (lactide-coglycolide) PLGA NPs for production using the displacement technique. The synthesized ETP-PLGA NPs were coated with galactose conjugate, shaken constantly, and then left to rest at room temperature for the whole night. The NPs were separated by ultracentrifugation at 34,000× g for 20 minutes.

Subsequently, the pellet had cleaned and was again suspended in distilled water. The synthesized NPs were characterized using a variety of techniques, including Fourier-transform infrared spectroscopy (FTIR), nuclear magnetic resonance (NMR), entrapment efficiency, size, zeta (μ)potential, polydispersity index (PDI), in-vitro drug release, and uptake studies.

The findings showed that the NPs had a positive ζ-potential, were 150–160 nm in size, and had sustained drug release for 32 hours. Furthermore, the NPs' entrapment efficiency was almost 70%. Chitosan (GC)-conjugated ETP-loaded poly (lactide-coglycolide) (PLGA) NPs were found to be 70% more effective at targeting RB than nonconjugated NPs, according to NPs uptake studies [97].

Hyaluronic Acid (HA) functionalized nanocarriers

Because it binds to the CD44 receptor, hyaluronic acid is a marine polymer that has received FDA approval and has excellent flexibility, biodegradability, shielding, and mobility in addition to its anticancer properties [98]. Retinal gene therapy is a novel treatment option for retinoblastoma that was developed in 2015 by Martens et al. In this study, HA was electrostatically coated onto nonviral polymeric gene DNA complex-based nanomedicines to create an anionic hydrophilic coating that enhanced intravitreal mobility. The resulting polyplexes with HA of various molecular weights were further assessed by the authors based on complexation, size, surface charges, and zeta potential. When HA concentrations were higher than when they were lower, it was found that the ζ-potential was four times more anionic. Following the development of an ex-vivo model using excised cow eyes and fluorescent single-particle tracking (FSPT), it was determined from the data that HA-coated

polyplexes exhibited enhanced mobility in intact vitreous humor and competent uptake via HA-based CD44-receptor endocytosis [99].

Folic Acid (FA) functionalized nanocarriers

When combined with a targeting moiety, nanocarriers can become more efficient in specifically eliminating malignant cells than systemic chemotherapy [100]. Site-specific administration of anticancer drugs is made possible by targeted moieties [101]. The folate receptor is the most often used targeting moiety in practical use. Because folate receptors are overexpressed in RB cells, using them to treat RBs will be very successful in destroying only cancer cells and allowing NPs to be absorbed selectively [102]. Chitosan NPs (CNPs) were synthesized by Parveen and Sahoo, and DOX was put into them [103]. Folic acid was conjugated with prepared NPs. The ionic gelation approach can be used to conjugate chitosan nanoparticles (CNPs) to DOX. The CNP pellets can then be collected by centrifuging the mixture at 18,000 rpm for 30 minutes at 4 °C. After being lyophilized and kept at 4 °C, CNPs were then mixed with distilled water, centrifuged at 3000 rpm, and coupled with folic acid using a coupling procedure.

Moreover, the conjugation of folic acid (FA) onto CNPs was examined using nuclear magnetic resonance (NMR) and Fourier-16-transform infrared spectroscopy (FTIR). The harmful effects of produced conjugated NPs were assessed in RB cells (Y-79) using the 3-(4,5dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay, a colorimetric method for evaluating cell metabolic activity. The outcomes demonstrated that conjugated NPs outperformed unconjugated DOX1-CNPs and pure DOX in terms of efficacy against RB cells. Furthermore, the mechanism of Y-79 cell apoptosis caused by DOX was evaluated. The results showed that in addition to initiating the mitochondrial pathways, FA-DOX-CNPs also caused the release of caspases and cytochrome c enzymes to aid in apoptosis.

Consequently, it was determined that FAtargeted NPs were a targeted, efficient, and long-lasting treatment for RB. Also, using a 22-factorial design, de MoraesProfirio and Pessine (2018) produced FA-conjugated chitosan-coated PLGA NPs for the safe and targeted delivery of carboplatin, improved the formulation, and evaluated by all the necessary optimal characterization procedures [104]. The results indicated that the NP yield was 92%, the encapsulation efficiency was 35.5%, the PDI was 0.20, the μ-potential was 46.0 mV, and the NP size was 178 nm.

Researchers created ligands based on polymers and sugar moieties to treat RB with multifunctionalized NPs, as was previously mentioned. Lectin-like sugar moieties were

present. When compared to healthy cells, RB shows a substantial overexpression of HA and galactose. Thus, compared to other ligands, overexpressed lectins offer a more potent targeting mechanism. Polymeric ligands, such as PLGA, were shown to be the most stable.

Lipid nanoparticles (LNPs)

One of the useful applications of nanotechnology is lipid nanoparticles (LNPs), which are used in cosmetics, nutraceuticals, and pharmaceuticals. Most of bioactive substances derived from lipids, such as carotenoids, fatty acids, flavonoids, tocopherols, polyphenols, and preservatives, are hydrophobic [105]. To ensure the stability of the formulations, all of the lipids listed above must be encapsulated as colloidal dispersions in the aqueous environment of the oil-in-water (o/w) type [106]. LNPs have become more significant in the treatment of infectious diseases, cancer, and heavy metal adsorption. The chosen chemotherapeutic agent for the treatment of RB is melphalan. But there is always a chance of immunogenicity and damaging healthy cells [107].

To overcome the limitations and guarantee optimal delivery and therapy, Tabatabaei et al. (2019) developed 171-nm switchable LNPs for the codelivery of melphalan and miR-181 with 93% encapsulation efficiency. 10% of the total lipid mixture was added to a melphalan and ethanol combination to create melphalan-loaded LNPs (LNP/melphalan). The LNPs were created by incubating them for 30 minutes at 40 °C while rehydrating with 5% dextrose in water after the ethanol was evaporated to produce a thin lipid layer. After that, miR181a was encapsulated and melphalan was measured. The efficacy of miR-181's encapsulation was indirectly assessed using the fluorescence displacement experiment. Formulated NPs were evaluated using a variety of characterization approaches, and the findings demonstrated that LNPs enhanced the production of apoptotic genes and had the greatest absorption and targeted killing of RB cells [108].

Nanoparticles of solid lipid (SLNs)

SLNs are adaptable lipid-based nanocarrier systems that have been improved by the complementary characteristics of polymeric particles, liposomes, and emulsions.

Solid lipid blends are used to create SLNs. These blends contain crystalline lipid droplets with a highly organized structure, which are made up of bioactive chemicals in the lipid matrix portion. The SLN lipid matrix's physical state can be managed to regulate the mobility of bioactive chemicals. Controlled drug release, drug targeting, effective encapsulation, and drug stability are among the benefits associated with SLNs [109,110,111]. To deliver etoposide to RB patients in a safe and targeted manner, Ahmad et al. (2019) synthesized SLNs. SLNs were

produced by ultrasonication and melt-emulsification procedures. To optimize the novel SLNs and ascertain the functional link between the response variables of particle size, 1 surface shape, and entrapment efficiency (EE), a three-factor levels Box-Behnken design was employed.

We also evaluated the SLNs' size, surface appearance, efficacy of trapping, and in vitro drug release. However, pharmacokinetic studies were carried out after the SLN formulation was injected intravitreal into Wister rats. In addition, a gamma scintigraphic analysis was performed to confirm that SLNs had been deposited in the albino rabbits' ocular tissues. In gamma scintigraphy, the bloodstream is filled with radiopharmaceuticals, also known as radioisotopes, which aggressively seek for seven necrotic or inflammatory tissues as well as damaged, healed, or irritated bone.

Histological studies were later carried out to evaluate the morphological changes and toxicity following therapy. However, the outcomes indicated that the optimized formulation's particle size, PDI, and EE were 239.43 nm, 0.261 ± 0.001, and 80.96% ± 2.21%, respectively. This formulation's ability to provide sustained drug release for seven days with just one intravitreal dose was its greatest advantage. The gamma scintigraphy study's findings also validated and verified the drug's sustained release over seven days. Histological investigations verified that the SLNs were nontoxic because they showed no negative effects on the posterior tissues of the eyes. It follows that etoposide-loaded SLNs are both safe and effective in the treatment of RB [112].

Nanoliposomes

When lipids come into contact with water, their hydrophobic system interacts with the water to cause the lipids to self-assemble by creating liposomes [113]. Liposomes are made up of an aqueous core that is surrounded by a lipid bilayer; they frequently become functional through ligand attachments [114,115]. In 2020, Zhao and colleagues manufactured cisplatin nanoliposomes to assess both in vitro and in vivo apoptosis in relation to RB cell lines. After Y79 cells were cultivated, apoptosis was evaluated by testing them with Annexin V and propidium iodide (PI). Flow cytofluorimetric analyses use the Annexin V/PI double staining kit to identify cell death. A highly sensitive technique for identifying cellular apoptosis is the Annexin V corresponding signal. On the other hand, propidium iodide (PI) is employed to identify necrotic or late apoptotic cells, which are identified by the nuclear and plasma membranes losing their integrity. The expression of Bcl-2 and Bax proteins was analyzed using western blotting, and the amount of caspase-3 in Y-79 cells was measured to determine whether

there had been any changes in inflammatory caspase-3. A tumor model was implanted in Y-79 using three sets (n = 5) of nude mice. The mice in the blank group received saline injection, whereas the nude mice in the control group received an injection of cisplatin. After the injections, the tumors were removed, and the naked mice were put to death. After removal, the overall volumes and weights of the tumors were compared. Furthermore, an in-situ cell death assay kit was used to evaluate apoptotic cells, and magnetic beads were used to extract DNA and RT-PCR for nucleic acid extraction.

In addition, upon analyzing the tumor reduction rate, the cisplatin liposome group demonstrated a significant increase in Y-79 apoptotic rate, caspase-3, decreased tumor volume and weight, and Bax protein expression in comparison to the cisplatin solution and dimethyl sulfoxide (DMSO) groups [116]. Researchers found that LNPs are the most promising for encapsulating hydrophobic medicines by increasing the oral bioavailability in this study, which used LNPs to treat RB. Several LNP (SLNs, liposomes, and core-shell nanostructures)-based approaches have been used in the past to successfully load anticancer medications; however, these approaches have had a number of drawbacks, including limited drug loading, instability, high cost, insufficient industrial scale, and the requirement for organic solvents. We think that the targeted destruction of RB should be combined with self-emulsifying carriers to lessen the negative effects of various lipid formulations. The ability of self-emulsifying drug delivery systems (SEDDS) to solubilize hydrophilic and hydrophobic drugs, along with their ease of manufacturing and thermodynamic and kinetic stability, has garnered them significant attention in the field of drug development and pharmaceutical technology.

Metallic nanoparticles

Chemotherapeutic chemicals are distributed randomly throughout the body, resulting in systemic toxicity and low patient compliance, making cancer therapy difficult. The field of cancer treatment greatly benefits from the use of metallic nanoparticles. In a similar vein, metallic nanoparticles can be used to treat rare forms of cancer like RB after active or passive targeting [117,118,119].

Silver nanoparticles (AgNPs)

Because of AgNPs' stable, affordable, green production, and visual qualities, they are frequently used in cancer therapies [120,121]. Remya et al. reported synthesizing AgNPs quickly using natural brown seaweed sources (Turbinaria ornate) and evaluating their cytotoxic potential against RB cells. AgNP synthesis was confirmed via UV-visible spectroscopy; other

characterization techniques included ζ potential, X-ray diffraction (XRD), Fourier transform infrared spectrum (FTIR), thermogravimetric analysis (TGA), potential, and high-resolution transmission electron microscopy (HR-TEM). With a total phenolic content of 43 nm, the generated AgNPs exhibited good scavenging efficiency.

Moreover, the cytotoxicity of the generated AgNPs against the RB Y-79 cell line showed a dose-dependent response at an inhibitory concentration (IC50) of 10.5 µg/mL. The results indicate that AgNPs are potential anticancer medications with enhanced ocular targeting and treatment [122]. In 2018, the same group of researchers added the polysaccharide laminarin to their Ag-NPs and extracted, purified, and analyzed laminarin using Matrix4 -Assisted Laser Desorption Ionization Time-of-Flight Mass Spectroscopy (MALDI-TOF MS), Proton Nuclear Magnetic Resonance (1H NMR), UV-vis, FTIR, XRD, and TEM. To evaluate the formulation's cytotoxicity against RB cells, free radical scavenging was also applied [123].

Gold nanoparticles (AuNPs)

Because AuNPs offer vast surfaces on which several functional molecules can be adsorbed, they have been sought after for their potential therapeutic benefits. Unfortunately, because of their toxicity, they have few uses [124-126,-]. In response to these issues, extracts from Vitus vinifera were used in the development of a green synthesis process by Kalmodia et al. (2017) for the manufacture of gold nanoparticles (GNPs) [127]. The produced GNPs were noncytotoxic and biocompatible. The mechanistic method of knocking down human double minute 2 (HDM2) functional protein cells was shown to require these NPs. Due to its ability to suppress the p53 tumor suppressor, HDM2 is a target for cancer. Because these HDM2 cells are overexpressed in retinoblastoma, they are killed down. Rosiglitazone-incorporated AuNPs were also created by Chen et al. (2020) for the treatment of human RB [128]. Through the use of flow cytometry, the anticancer activity, proliferation, and apoptosis of retinoblastoma cells were examined. Moreover, the potential regulatory function of rosiglitazone AuNPs via the PI3K/Akt pathway was investigated using phosphoinositide 3-kinase inhibitors (PI3K inhibitors). The findings showed that, in comparison to the untreated controls, the synthetic formulation dramatically lowered retinoblastoma cell proliferation, antitumor activity, and apoptosis. In 2020, Wang and colleagues created multifunctionalized NPs for low-intensity focused ultrasound-assisted imaging, which can be employed for both the diagnosis and synergistic therapy of RB. This innovative formulation is the result of the conjugation of magnetic hollow mesoporous gold nanoparticles (AuNCs) with iron oxide nanoparticles (Fe3O4). The produced conjugated (AuNCs14 Fe3O4) nanoparticulate system was then

modified to encapsulate the perfluoropentane (PFP) and muramyl dipeptide (MDP), as shown in Figure 2. The produced nanoparticulate conjugate was successfully characterized by TEM, FT1 IR, loading efficiency, release, in-vitro cytotoxicity, apoptosis, magnetic targeting ability, in-vivo therapy, and biocompatibility.

The comprehensive biosafety assessment is one of the most crucial aspects of multifunctional nanoparticle characterization. The findings showed that multifunctional magnetic AuNCs-Fe_3O_4/MDP/PFP nanocarriers improved magnetic resonance and photoacoustic imaging. After these nanocarriers' directed penetration, a magnetic field causes them to collect inside the tumors, whereupon MDP is released during phase change and radiation. Following its release, MDP encouraged dendritic cell maturation and activation, enhancing their capacity to recognize and eliminate tumor cells. This has significant potential as an improved treatment outcome against RB [129]. To lessen RB malignancy, scientists have created metallic nanoparticles (silver and gold), yet these particles have serious toxicity problems. We believe that the green manufacturing of metallic nanoparticles can be promoted to provide non-toxic anticancer efficacy.

Conclusion

There is a lot of promise in employing nanoparticle drug delivery methods to target retinal cancer cells with chemotherapy medicines. When compared to traditional treatment methods, nanoparticles that were evaluated to target retinoblastoma cells generally showed higher uptake and intracellular internalization, prolonged retention, great cytotoxicity, greater apoptosis, and an improved antitumor impact. This review unequivocally demonstrates the superior anticancer activity of delivery strategies based on nanoparticles in retinal tumors. Additionally, it validates the excellent potential of nanoparticles, which ought to be utilized for retinal tumors diagnosis and treatment. The possible approach to addressing some of the obstacles in antitumor and imaging compound administration is the use of intelligent nanoparticles to specifically target tumor cells. Therefore, the creation of tailored systems for drug delivery based on nanoparticles may enhance the diagnosis, boost the effectiveness and safety of chemotherapy, enhance the quality of life, and raise the percentage of RB patients who survive. This study described imaging of the eyes. The ultimate goal of creating "intelligent nano systems" to combat powerful, fatal intraocular tumors should be accomplished by creating combinatory techniques that accommodate various design constraints.

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