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REVIEW

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Nanotechnology-based strategies overcoming the challenges of retinoblastoma: a comprehensive overview and future perspectives

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Abstract

Background Retinoblastoma (RB) is a rare type of pediatric ocular cancer with difficulty in treatment and detection owing to alterations in tumor suppressor genes and the lack of focused, efficient, and cost-effective treatments.

Main body of the abstract The current review presents different approaches adopted for the treatment of RB. Recently, nanodrug delivery-based systems have shown significant reported advancements in RB treatment owing to their effectiveness in delivering their cargo to the site of tumor growth, where they may induce programmed tumor cell death. Among various nanoparticulate systems employed in RB treatment are organic nanoparticles, lipid-based nanocarriers, polymeric nanoparticles, inorganic (metallic) nanocarriers (cerium oxide, iron oxide, gold and silver), and surface-tailored multifunctionalized nanocarriers.

Short conclusion The current review article aims at demonstrating the superiority of nanotechnology-based formulations to traditional therapies for treatment of RB in order to enhance the bioavailability and targeting of drugs to posterior eye segment specifically, thus improving patient compliance and adherence to treatment by minimizing the number of dosing intervals and hence the likelihood of side effects.

Keywords Retinoblastoma, Children, Rare ocular cancer, Posterior eye segment targeting, Conventional treatments, Nanoparticles

Background

Anatomy of the eye

Briefly, the eye is composed of two segments: anterior and posterior segments. The anterior segment comprises (a) Iris which controls the amount of light entering the eye. In front of the lens, the pigmented region of the eye is visible [1], (b) Eye pupil which is the opening in the center of the iris via which light enters the eye lens. The iris controls the pupil's dilation and constriction [2], (c) Cornea, the transparent round anterior segment of the eyeball refracting incoming light onto the lens, which then directs the light to the retina. The cornea lacks blood vessels and has a high threshold for pain [3], and (d) Lens, a translucent structure behind the pupil. It is contained in a thin, transparent capsule and aids in the refraction and concentration of incoming light on the retina [4]. The posterior segment comprises (a) Choroid which separates the sclera and the retina. Additionally, it has a pigment that absorbs excess light to prevent blurred vision [5], (b) Ciliary body which connects the choroid to the iris [6], (c) Retina, a light-sensitive layer

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lining the interior of the eye, which is composed of rod and cone cells that are sensitive to light [7–9], (g) Optic nerve includes all visual information which is transmitted to the brain [10, 11] and (h) Sclera, the white portion of the eye, representing the protective outer layer of the eye formed by the cornea [12].

Etiology of RB

RB (Fig. 1) is a rare and aggressive, can be hereditary ophthalmological pediatric cancer [13]. Its incidence worldwide is 1/16000–1/18000 live births [14], which translates to around 8000–9000 new cases on annual basis, or 3–4% of all malignancies in pediatrics [15]. It is widespread among children under the age of five, with a prevalence of 1 in 15,000 [16, 17].

The prognosis for this condition is poor in around 80% of patients in low- and middle-income countries [18], due to poor health regimens and a lack of early detection; however, the survival rate is close to 100% in high-income countries [19]. Mutations in chromosome 13q14.2 result in the manifestation of RB in the first years of life [20]. The tumor suppressor gene RB1, located on chromosome 13q14.2 with aberrant phenotypic expression, is used to genetically characterize RB [21]. RB only occurs when both copies of the RB1 gene are abnormal functioning or absent [22].

The "two hit" hypothesis postulates that mutations at the germinal stage, which impact all retinal cells, resulting in cell cycle abnormalities and erroneous entrance into S phase of the cell cycle, may be the reason of RB [23]. RB may be hereditary or develop spontaneously. Bilateral RB (inherited RB) is caused by two mutations that occur before fertilization, causing malignancy to manifest at a younger age and often proceeds to bilateral RB [24].

In the spontaneous type of RB (unilateral RB), somatic mutations predominate, and both mutations develop in a single retinal cell following fertilization. This type of cancer usually occurs in the later years, and is not usually transmitted to the off springs [25].

The growth of RB tumors, developing from immature retinal cells, depends on the existence of different types of vasculatures. The tumor spreads as seeds (white mass) toward the vitreous and/or sub-retinal area. Although the seeds are avascular, the primary tumor is vascularized [22].

The retina's inner layer is made up of neurons that are sensitive to light [26]. These cells are linked to the brain through the optic nerve. Without prompt treatment, devastating consequences may occur, including loss of vision, secondary non-ocular cancers, and even death. In severe cases, changes in iris color and eye enlargement caused by high intraocular pressure may occur. The eye's unique anatomical and physiological structures offer an extensive barrier to drugs' delivery to diseased regions of the eye [27].

The blood retinal barrier (BRB), involved in the maintenance of ocular homeostasis, is another barrier to the transport of drug molecules into the eye [28]. The main parts of the BRB that allow solutes to cross from the blood to the retina comprise retinal pigment, retinal capillaries, sclera, and choroid. Retina is a part of the CNS, like the brain. As a result, tight junctions maintain retina's normal function in addition to the crucial oxygen consumption rate and glycolysis [29–31].

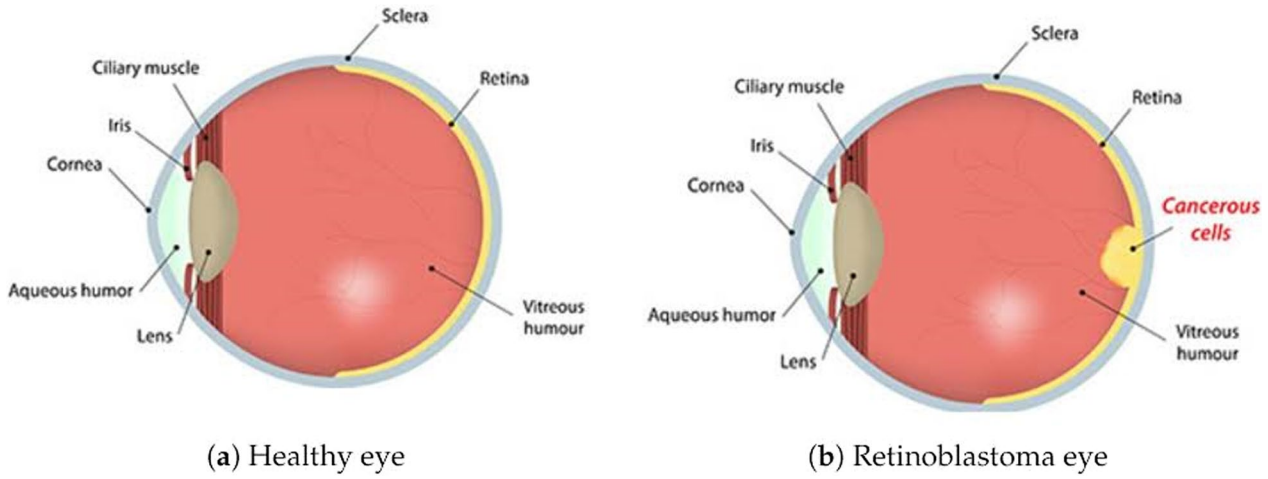

Fig. 1 Comparison between **a** healthy eye and **b** retinoblastoma eye [15]

Diagnosis and prognosis

Symptoms of RB include leukocoria (white pupil), strabismus (misaligned eyes) and reflection in the eye of the child. Changes in the iris color and larger eyes owing to increased intraocular pressure are common in advanced stages [32]. Detection, early medical intervention, involving a multidisciplinary team of radiologists, oncologists, geneticists, ophthalmologists, and suitable radiation, chemotherapy, and surgical treatments are necessary for the long-term improvement of patient life [33].

The diagnosis may usually be made using indirect ophthalmoscopy and pharmacologically dilated pupils. Ocular ultrasonography (β-scan) may be utilized to identify RB calcifications; however, MRI is required to assess trilateral RB and optic nerve invasion. Computed tomography should not be used on patients with RB1 mutations as radiation causes secondary malignancies [34, 35].

Alternatively, biopsies might provide crucial details on the histological type of ocular malignancy; however, sampling errors may lead to false negative results [36]. The development of ocular molecular imaging, which permits the early diagnosis of this eye disorder before the formation of any morphological abnormalities, is urgently needed despite the availability of numerous ophthalmic imaging techniques [37]. Fluorescein angiography, needle biopsy, ultrasonography, MRI, and CT are often used by physicians to identify RB based on the presence of retinal tumors [14].

Different treatments are used depending on how the tumor is progressing. However, in more severe cases of the disease, the whole globe and its intraocular contents must be surgically removed (enucleation), while in other cases; conventional treatments are employed [38].

For attaining best therapeutic efficacy and prognostication, RB must be classified. The original categorization was proposed by Reese–Ellsworth in 1963 [39]. Thereafter, in 2005, Murphree's International (IIRC) categorization [40], divides this ocular tumor into five groups (from A to E, with E being the most severe) [41]. Finally, this categorization was somewhat amended by the Children's Oncology Group (COG) [42].

The need for primary enucleation or conservative treatment may rely on the clinical status of the patient. All patients who have unilateral or bilateral RB of groups A, B, C, and D are eligible for specific therapy, however individuals who have bilateral RB of group E are only eligible for conservative treatment [43]. A direct biopsy cannot be used to diagnose RB in order to stop the development of metastases and the spread of disease outside the eye [35].

Main text

Different modalities for treatment of RB

To treat RB, anticancer drugs have been injected via the intravitreal, subconjunctival, topical, systemic or subtenon routes. Although these delivery systems are successful in managing the eye's anterior area, they have been ineffectual in treating the disorders of the eye's posterior segment where RB originates [44].

Different therapeutic procedures may be employed (Fig. 2), depending on the stage of the disease. Systemic chemotherapy is frequently used in conjunction with local treatments (for example, cryotherapy, photocoagulation, brachytherapy, laser, radiotherapy, hormonal, and thermotherapy). In severe cases, surgery is frequently required to remove the whole globe and its intraocular components (enucleation) [45].

The absence of a relationship between the outcomes of in-vivo research and in-vitro test findings is one of the obstacles to the development of cancer treatments.

Conventional treatment of RB

For the treatment of RB, several approaches have been presented. In the past, RB treatment was based on the administration of aggressive focused treatments in addition to systemic chemotherapy and beam radiation (EBRT) [46, 47]. The use of EBRT in particular has been reduced lately due to a number of adverse side effects that occurred including ototoxicity, leukemia, and future primary neoplasms. EBRT was widely utilized up until the beginning of the twenty-first century [48, 49].

For these reasons, selective ocular delivery systems capable of augmenting the drug's effectiveness while decreasing the likelihood of side effects have been developed over the last decade. RB treatment is now tailored to the tumor's site (intraocular and/or extraocular disorders) and is meant to preserve vision. Moreover, patients with intraocular diseases, especially those related to bilateral ocular disorders, may have a high incidence of ocular protection when applying conservative tumor reduction using intravitreous chemotherapy (IVi) or ophthalmic artery chemosurgery (OAC) combined with extensive local treatment. Nowadays, radiation therapy is only used in cases of extraocular or intraocular disease progression [50, 51].

The conservative treatment is often associated with intense and early focused treatments, using conventional chemotherapeutic agents (i.e., Etoposide, Carboplatin, Palbociclib, Cisplatin, Cyclophosphamide, Doxorubicin, Melphalan, Vincristine, and Topotecan) at different durations and doses depending on the intraocular stage [22].

A physiological barrier, blood retinal barrier (BRB), regulates the flow of proteins, ions, and water inside

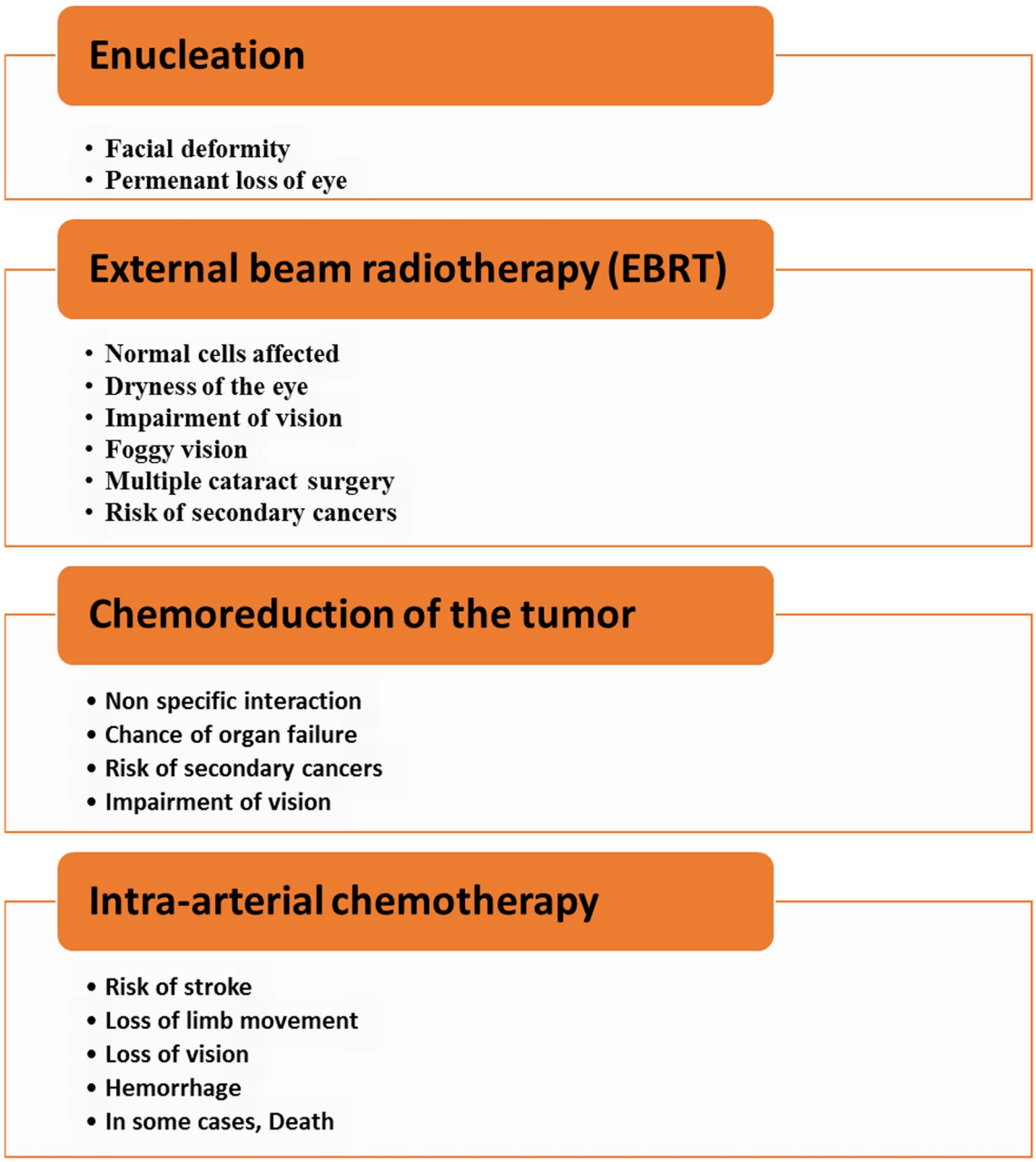

Fig. 2 Different modalities used to treat RB and their drawbacks

and outside the retina [52]. The use of conventional anticancer drugs is accompanied by a number of adverse effects such as sores in the mouth and on other mucous membranes, hair loss, bone marrow toxicity, cardiac anomalies, and severe nausea and vomiting, besides, their efficacy is hampered by their inability to penetrate the BRB. Intra-arterial chemotherapy has often been employed to manage this problem [4, 53]. The ophthalmic artery and the femoral artery are both inserted with a micro-catheter as part of this method, and chemotherapeutic agents are then infused in a pulsatile manner [54].

Complications accompanying conventional treatment modalities include ophthalmic artery blockage, partial choroidal ischemia, branch retinal artery obstruction, visual neuropathy, ophthalmic artery spasm with reperfusion, vitreous hemorrhage, and in certain circumstances, patient death [55–57].

Drug discovery for RB treatment

Despite advances in treatment of RB, this disease may still be challenging to treat in certain refractory cases. As a result, researchers are now working to identify novel drugs that can cure both RB and intraocular malignancies utilizing two essential methods [58]:

(i) Large-scale chemical high-throughput screening (HTS) employing cells.
(ii) Repurposing of approved drugs for other types of cancers.

Pharmacokinetic features (such as solubility, metabolism, and the capacity to cross the BRB) are regarded as crucial for the targeting of drug molecules and the design of drug delivery systems. With a focus on evaluating drugs on primary cell lines generated from cerebrospinal and intraocular fluids in which RB metastases, HTS has been used. Additionally, animal models with tumors xeno-grafted from intraocular or metastatic RB may be helpful for developing an effective treatment for humans [59].

Nutraceutical agents

In recent years, various naturally occurring agents have been demonstrated for RB treatment in addition to conventional anticancer drugs such as catechol derivatives (as curcumin), sterol derivatives (as ursolic and oleanolic acid), and naphthoquinones (as β-lapachone) [60]. Among these nutraceuticals is ARQ-501 (β-lapachone), an ortho naphthoquinone derivative, isolated from a tree whose extract has been used in medicine for generations, has been utilized for treatment of ocular tumors [61]. Although its exact mechanism of action is still unknown, several studies have shown its efficacy to block topoisomerase enzymes, resulting in DNA damage, cell cycling arrest, or even cell death. According to the latest studies, it may be advantageous in treating a variety of disorders, including cancer [62]. β-lapachone is now being assessed in fourteen clinical trials, primarily for solid tumors (such as pancreatic cancer, adenocarcinoma, and head and neck neoplasms), and for lymphoma [63].

Moreover, Celastrol, a Chinese herbal drug, showed its effectiveness against several tumor cell lines for treatment of RB. A previous study reported that effectiveness of Celastrol in promoting dose-dependent apoptosis in SO-Rb50 human RB cells [64].

Routes of drugs' administration to posterior eye segment

The efficacy and safety of the drug are highly influenced by the route of administration. Modifying the administration route may boost and extend the therapeutic results. Delivery systems must be tailored to each administration route since each has its own pros and cons to transport drugs effectively and correctly [65, 66]. Different routes and modes of drugs' administration to posterior area of the eyes are discussed thoroughly in Table 1.

Nanotechnology-based approaches for treatment of RB

Ocular cancer treatment has employed topical, systemic, intravitreal, and sub-conjunctival administration techniques. These delivery systems are beneficial for the anterior segments of the eye; however, they have not shown significance in treating disorders (such as RB) at the posterior segments of the eye [44, 67].

Nanodrug delivery systems (Fig. 3) can provide sustained drug release to maintain therapeutically effective concentrations over time, efficient drug targeting and augmentation of pharmacokinetics, pharmacodynamics, toxic, and immunogenic features, thus ensuring increased efficacy for treatment of ocular disorders [68, 69].

The beneficial properties of nanoparticles (NPs), or particles with sizes between 1 and 1000 nm, have led to their widespread use in medicine. Since NPs are so tiny, they can penetrate cells, having a high surface area-to-volume ratio that amplifies all surface phenomena, thus causing little harm to cell membranes and surrounding cells [71].

Increasing penetration into the retinal pigment endothelium layer, that limits the transport of drugs into the tumor site, is a significant criterion for RB's nanodrug delivery systems. Nanodrug delivery improves the efficiency of cytotoxic anti-cancer drugs by decreasing their toxicity and non-specific interactions and increasing the solubility of weakly water-soluble therapeutic molecules [72]. As indicated in Table 2, many nanoparticulate systems have been utilized for the treatment of RB such as organic, inorganic, multifunctionalized nanocarriers and others. A summary of nanotechnology-based systems used for the management of RB is discussed in the upcoming lines.

Organic NPs

Organic nanoparticles are assemblages of organic molecules with an almost infinite number of distinct configurations. They are frequently produced by non-covalent intermolecular interactions, rendering them more malleable in nature and providing a route for elimination from the body. Owing to their flexibility, these nanoparticles can alter shape or conformation when exposed to external stimuli [73]. In RB treatment, the most common type of organic NPs are lipid-based nanoparticles (LNPs), lactoferrin nanoparticles and polymer-based (e.g., polycaprolactone (PCL), chitosan (CH), polylactic-*co*-glycolic acid (PLGA), and polymethylmethacrylate (PMMA) NPs), showing biocompatibility, high bioavailability in RB

Table 1 Routes of drug delivery to the posterior segment of the eye

Delivery route		Advantages	Disadvantages	Present FDA and research approved examples	Ref.
Systemic	Oral	Simplicity of use	Systemic adverse effects		[8]
	IV	Low cost Good Patient compliance Minimal systemic adverse effects	Low ocular bioavailability (1-2%)	Intravenous administration of PLA-PEG chains with cell-penetrating peptide nanoparticles enhanced light-triggered local delivery of drug to the infected choroid * Intravenous nanoparticles loaded with doxorubicin dramatically reduced the size of neovascular lesions *	[12]
Topical	Ointment	Low cost	Therapeutic doses can't be delivered to the retina owing to the existence of dynamic and static barriers	A dexamethasone-eluting contact lens achieved sustained therapeutic levels of dexamethasone to the retina 200-fold greater than hourly administered dexamethasone drops *	[127]
	Eye drops	Simplicity of use	Low therapeutic efficacy with amount less than 5% of the drugs diffusing through the eye following administration	An *in situ* thermosensitive hydrogel decreased laser-induced choroidal neovascularization in the posterior segment of the eyes of rats and pigs*	[100]
	Gels	Low systemic side effects		DEXTENZA®, a dexamethasone intra-canalicular inserted into the lower lacrimal punctum, showed good effectiveness in treating pain and ocular inflammation during eye surgery along with ocular itching accompanied by allergic conjunctivitis **	[126]
	Eye Drops with nano/micro systems	Easily fabricated Good patient compliance			[103]
Peri-ocular	Injections or implants inserted within the orbital rim of the eyeball (ex: sclera)	Less invasive, with less risks and retinal impairment, compared to intravitreal injections.	Lower concentrations are attained as compared to intravitreal injections/ implants	An iontophoretic hydrogel device improved the transport of intraocular nanoparticles and macromolecules to posterior eye segments *via* trans-scleral channels up to 300 times *	[127]
Intra-cameral	Implants or injections administered to the anterior segment of the eyeball	Cost-effective and efficient The optimal drug's dosage is administered. Reduced systemic and ocular surface adverse effects in comparison with topical administration Circumvents the challenging barrier of the cornea.	Possibility of triggering toxic anterior segment syndrome. Endothelial cells of the cornea may be harmed. Invasive method.	DURYSTA™, an FDA approved biodegradable intra-cameral implant, containing bimatoprost for the management of ocular hypertension patients ** DEXYCU™, the first FDA-approved anti-inflammatory drug for use after cataract surgery using dexamethasone intra-cameral injectable suspension **	[128]

Table 1 (continued)

Delivery route		Advantages	Disadvantages	Present FDA and research approved examples	Ref.
Suprachoroidal	Microneedles	Higher bioavailability than periocular routes	Potential tissue damage	XIPERE®, an injectable suspension of triamcinolone acetonide administered into the suprachoroidal space (SCS) ** Microinjector®, an FDA-approved delivery system, given to SCS®, and used for the management of uveitis macular edema **	[13]
	Suprachoroidal injected in situ gel	Targeting with high bioavailability in the retinal pigment epithelium and choroid.	Fabrication difficulty	In rabbit eyes, a microneedle-based device aided by iontophoresis boosted posterior targeting with efficiency more than 30% compared to nanoparticles in the SCS *	[77]
Intravitreal	Injection	Increased drug concentrations in vitreous and retinal regions.	Painful	Ozurdex®, an intravitreal FDA approved dexamethasone biodegradable implant used for the management of uveitis and diabetic macular edema **	[124]
	Implant	Minimal systemic side effects	-Frequent injections can cause complications -Difficulty in implant's application and removal -Implant may result in acidity in the microenvironment	ILUVIEN®, an approved non-biodegradable, injectable corticosteroid implant comprising Fluocinolone acetonide used for the management of macular edema**	[122]

*The described study is a pre-clinical trial

**The described study is an approved market product

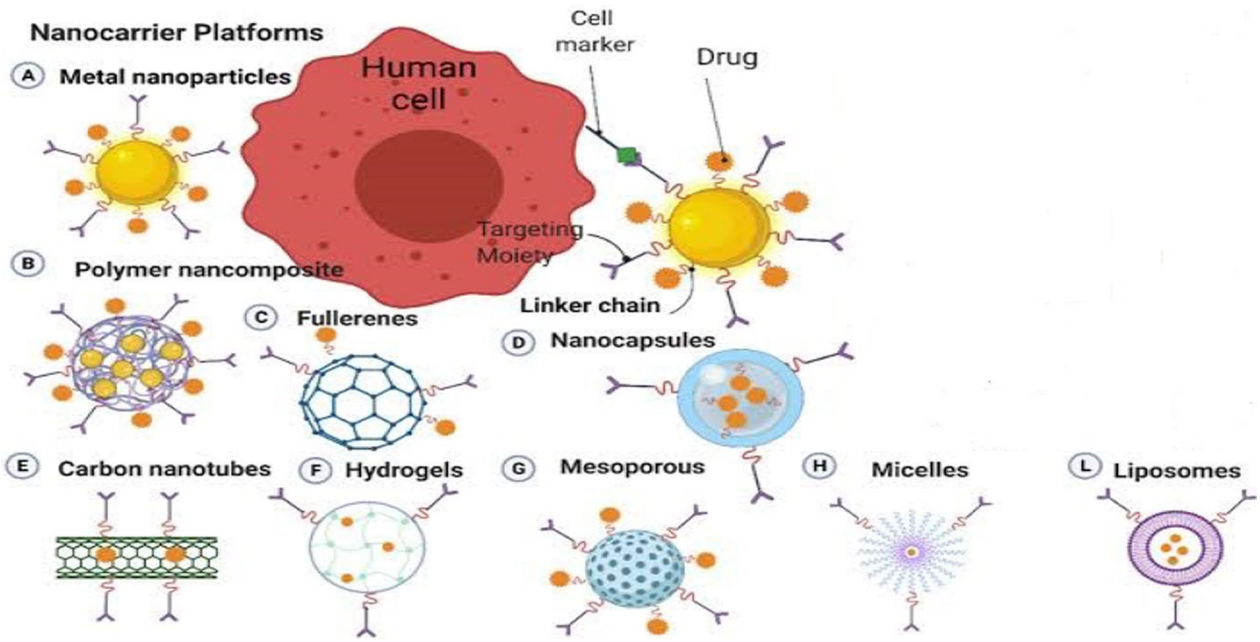

Fig. 3 A schematic diagram showing nanotechnology-based drug delivery systems for the treatment of ocular disorders [70]

cells, with no discernible toxicity besides excellent photothermal and photoacoustic imaging characteristics. Their photothermal properties allow them to absorb light energy and transform it into heat, raising the temperature of the surroundings and causing the death of ocular cancer cells. They can also enable the selective targeting of tumor cells, minimizing the damage to adjacent healthy tissues. The photothermal effect, in addition to destroying cancer cells, can generate acoustic waves that can be detected and turned into imaging signals, a process known as photoacoustic imaging. The method not only gives an additional imaging technique for RB diagnosis, but it also allows for the identification of various biologically relevant signals in a tumor microenvironment, such as reactive oxygen species (ROS), acidic pH, and certain enzymes [74].

A recent study by Mudigunda et al. [75] demonstrated the effectiveness of hybrid PLGA/PCL NPs encapsulating Palbociclib (PCB), as anticancer agent, together with a photothermal dye on Y79 RB cells with higher drug bioavailability in these cells compared to drug control. Furthermore, Sims et al. [76] demonstrated the effectiveness of surface-tailored PLGA-NPs carrying melphalan for intra-arterial treatment of RB, paving the way for *in-vivo* application. Additionally, Silva et al. [77] investigated PLGA nanoparticles sequestering ursolic acid (UA) and oleanolic acid (OA) as a single-dose combination therapy for the management of RB. PLGA-OA/UA nanoparticles showed potent cytotoxic potential against the Y-79 cell line delineating these NPs as a promising approach for treating RB. Moreover, another study documented the efficacy of clinical-grade carboplatin and etoposide-loaded lactoferrin nanoparticles on RB y79 in terms of increasing drug retention, uptake and cytotoxicity compared to their standard drugs [78]. Furthermore, Ahmed et al. [79] demonstrated the potential of carboplatin loaded lactoferrin nanoparticles to enhance ocular drug's retention and intracellular uptake and accordingly, resulting in high anti-proliferative activity into the RB cells compared to the drug alone.

Lipid NPs (LNPs)

Lipid nanoparticles have shown to be promising ocular drug delivery systems since they comprise natural excipients and can incorporate lipophilic drugs, in addition to their distinctive characteristics such as good biocompatibility, safety, and adhesion, which allow for increased bioavailability, compliance, and prolonged drug release. LNPs are useful nanotechnology-based systems used in drug delivery to manage different types of ocular disorders including RB. LNPs gained more attention in the treatment of infectious diseases and cancers, besides the absorption of heavy metals [72].

A previous study reported the effectiveness of switchable LNPs for the co-delivery of melphalan and miR-181 with good efficacy against RB [80]. Furthermore, N'Diaye et al. [81] created LNPs composed of a poly(D, L)-lactide (PDLLA) nanoparticle grafted with a phospholipid (1-palmitoyl-2-oleoyl-sn-glycero3-phosphocholine/1,2-dioleoyl-trimethylammonium propane) bilayer

Table 2 Summary of the nanocarriers employed in the treatment of RB

Nanodelivery system	Studies	Ref
Organic nanoparticles	Mudigunda et al. reported the effectiveness of hybrid PLGA/PCL NPs loading Palbociclib as well as a photothermal dye on Y79 RB cells with higher drug bioavailability in these cells compared to drug control	[78]
	Sims et al. demonstrated the effectiveness of intra-arterial surface-tailored PLGA-NPs carrying melphalan for RB management paving the way for *in-vivo* application	[79]
	Silva et al. demonstrated that PLGA-ursolic acid/oleanolic acid nanoparticles showed strong cytotoxic activity against RB cell line	[80]
	Narayana et al. documented the efficacy of clinical-grade carboplatin and etoposide-loaded lactoferrin nanoparticles on RB y79 in terms of increasing drug retention, uptake and cytotoxicity compared to their standard drugs	[81]
	Ahmed et al. demonstrated the potential of carboplatin loaded lactoferrin nanoparticles with high anti-proliferative activity into the RB cells compared to the drug alone	[82]
Lipid nanoparticles (LNPs)	Xu et al. reported the efficacy of switchable LNPs for the co-delivery of miR-181 and melphalan with good efficacy against RB	[83]
	N'Diaye et al. demonstrated the efficaciousness of LNPs incorporating beta-lapachone and temoporfin against RB Y79 cells, in which they could be supplied in a single intravitreal injection for treatment of RB	[84]
Solid lipid nanoparticles (SLNs)	Ahmad et al. showed the effectiveness of injectable etoposide SLNs for achieving safe and targeted drug against RB	[87]
Nanostructured lipid carriers (NLCs)	Almedia et al. reported the effectiveness of an eye drop containing ibuprofen dispersion encompassing a combination of NLCs and a thermo-responsive polymer with considerable cytotoxicity, improved bioavailability, and therapeutic effectiveness, besides sustained-release drug profiles	[89]
Doxorubicin (DOX)-loaded poly-B-hydroxybutyrate microspheres	Hu et al. showed the functionality of these microspheres to extend DOX release to the posterior eyes' segment	[96]
Carboplatin hyper-branched PAMAM dendritic nanoparticles	Kang et al. proved the potential of carboplatin loaded on dendrimer type PAMAM to increase carboplatin's bioavailability which inhibited toxicity and tumor mass in RB compared to free carboplatin	[97]
	Makky et al. proved an enhanced targeting and reduced toxicity outcomes when loading concanavalin in dendritic nanoparticles for treatment of intraocular tumors and RB	[98]
Polymeric nanoparticles	Arshad et al. proved that the successfulness of chitosan nanoparticles for delivering DOX to the Y79 RB cell line with increased folate receptor concentration	[100]
	Delrish et al. demonstrated the augmented efficacy of thiolated chitosan nanoparticles comprising topotecan relative to free topotecan in Y79 RB cells	[101]
	Delrish et al. demonstrated increased ocular bioavailability of thiolated chitosan carboxymethyl dextran nanoparticles in retinoblastoma induced rat eyes	[102]
	Godse et al. revealed that galactose conjugated chitosan nanoparticles loaded with etoposide exhibited greater cytotoxicity and resulted in higher apoptosis in RB Y-79 cells relative to pure etoposide	[103]
	Mohseni et al. demonstrated that lauric acid-grafted chitosan-alginate nanoparticles incorporating melphalan enhanced its penetrability to the vitreous cavity with augmented efficacy, delineating their potential for RB treatment	[104]
	Boddu et al. reported that a micellar system comprising DOX exhibited a two-week continuous release of the drug and a fourfold increase in cell absorption over the free drug	[105]
	Das and Sahoo emphasized that folate-tagged PLGA nanoparticles containing curcumin and nutlin-3a were able to reverse multidrug resistance (MDR) pathways and increase cancer cell apoptosis, expanding therapeutic efficacy for RB treatment	[106]
	Rebibo et al. revealed the superior efficacy of tacrolimus-loaded PLGA nanocapsules for RB treatment in augmenting drug's retention and enhancing penetration to posterior eye compartments	[107]

Table 2 (continued)

Nanodelivery system	Studies	Ref
Silver NPs (AgNPs)	Remya et al. reported the cytotoxic efficiency of AgNPs derived from natural sources of brown seaweed Turbinaria ornata against RB cells	[110]
	Rajanahalli et al. revealed that AgNPs resulted in cell cycle arrest in G1, and S phases mediated by repression of RB protein phosphorylation using stem mouse embryonic stem cells	[111]
Gold NPs (AuNPs)	Wang et al. proved the cytotoxicity of gold nanocages linked with iron oxide NPs in retinal pigment epithelium cells and RB Y79 cells, indicating that the system was physiologically safe and potential for further use	[113]
Iron oxide NPs	Demirci et al. revealed that magnetic hyperthermia in the Y79 RB cell line utilizing dextran-coated iron nanoparticles resulted in the apoptosis of 46% to 73% of Y79 RB cells	[114]
Mesoporous silica NPs (MSNPs)	Gallud et al. reported the efficacy of functionalized mesoporous nanoparticles loaded with camptothecin in treating RB using Y79 cells	[117]
	Qu et al. demonstrated that carboplatin loaded in MSNPs increased cancer cell death in RB cells compared to free carboplatin	[118]
	Gary-Bobo et al. showed the effectiveness of camptothecin, mannose, or galactose in MSNPs against Y-79 RB cells	[119]
	Warther et al. reported the efficacy of mannose-functionalized MSNPs for targeting and imaging RB cells	[120]
Cerium oxide NPs (CeONPs)	Stephen and Chen displayed the efficacy of CeONPs in inhibiting the apoptotic signaling pathway of RB Y78 cell lines, increasing the expression of genes associated with neuroprotection	[122]
	Gao et al. demonstrated the efficacy of glycolic chitosan-coated cerium nanoparticles loaded with DOX in the significant inhibition of tumor growth as well as the biocompatibility of the proposed NPs with normal retinal cells *in-vivo*	[124]
	Kartha et al. revealed the superiority of cerium-doped titanium dioxide nanoparticles in augmenting anticancer cytotoxicity compared to titanium dioxide nanoparticles	[125]
Surface-modified Melphalan nanoparticles	Farhat et al. revealed that surface-modified melphalan nanoparticles exhibited superior association and effectiveness against RB cells for RB intravitreal chemotherapy	[128]
Galactose-functionalized nanocarriers	Godse et al. reported that etoposide loaded PLGA nanoparticles coated with chitosan and galactose improved the drug's cellular internalization, promoting superior anti-cancer activity	[100]
Hyaluronic acid (HA)-functionalized nanocarriers	Martens et al. reported that the formulation of electrostatically coated nanoparticles incorporating nonverbal polymeric gene DNA complexed with HA provided increased intravitreal mobility in RB cells	[126]
Folic acid (FA)-functionalized nanocarriers	Mitra et al. reported that DOX conjugated with folic acid proved their efficacy for targeting RB cells	[128]

incorporating beta-lapachone as an anticancer agent and photosensitizer, temoporfin, for combined photodynamic and chemotherapy therapy against RB Y79 cells. The investigated system was shown to be efficacious in both chemotherapy and photodynamic treatment and could be supplied in a single intravitreal injection for treatment of RB.

Solid lipid NPs (SLNs)

SLNs represent lipid-based nanocarriers that combine the advantages of emulsions, liposomes, and polymeric particles. To create SLNs, solid lipid matrixes that combine crystalline, highly structured lipid droplets containing bioactive agents, are employed. It is possible to regulate the entrapment of bioactive compounds by changing the SLN lipid matrix's physical state. SLNs provide targeted ocular drug delivery, regulated drug release, and drug stability [82, 83]. A previous study conducted by Ahmad et al. [84] reported the effectiveness of SLNs for the targeted and safe etoposide's injection against RB.

Nanostructured lipid carriers (NLCs)

NLCs are the second generation of SLNs, designed by substituting liquid lipids for the fractional solid lipid components of SLNs, causing an expanded drug corporation space. NLCs are superior to traditional carriers

for ocular drug delivery in a number of ways, including improved solubility, the ability to increase storage stability, enhanced bioavailability and permeability, longer half-life, fewer side effects, and tissue-specific delivery [13]. Table 3 provides a comparison between the pros and cons of NLCs and SLNs for ocular drug delivery [85].

Almedia et al. [86] designed an eye drop dispersion of ibuprofen that comprised a combination of NLCs and a thermo-responsive polymer possessing muco-mimetic properties. The cytotoxicity of the formed dispersion was then tested on Y-70 human RB cells, and considerable cytotoxic potential was found. The cytotoxicity of NLCs was then tested using the Alamar Blue reduction assay, which revealed that they were harmless. Later, the results showed that ibuprofen exhibited enhanced bioavailability and therapeutic effectiveness, together with sustained-release drug profiles when loaded in these nanoparticles.

Nanovesicular delivery systems

Nanovesicles comprise an aqueous core enclosed by a lipidic bilayer membrane. Many pharmaceutical enterprises, including those in cancer therapy, employ these systems to encapsulate therapeutic compounds [87].

Liposomes

One of the most popular vesicular systems employed for the management of posterior eye segment disorders is liposomes. Amphipathic phospholipid-based vesicular structures known as liposomes may encapsulate both hydrophobic and hydrophilic molecules [88].

Despite their vulnerability to surface alterations, liposomes have been frequently employed to carry chemotherapeutic agents. Till the current date, no studies have been performed using liposomal systems for the management of RB. However, other studies reported the efficiency of liposomes for the delivery of fluorescein isothiocyanate (FITC) tagged polystyrene or fluorescent probes coumarin-6 to the retina owing to liposomal small particle size, facilitating its permeation across the BRB [89].

Polymeric nanoparticles (PNPs)

Polymeric nanoparticles are particles ranging in size from 1 to 1000 nm that can be laden with biologically active substances which are surface adsorbed onto or entrapped within the polymeric core. They comprise various kinds of polymers, used to produce nanocapsules or nanosphere (Fig. 4). Nanocapsules are reservoir-type systems where the drug is encapsulated inside a cavity surrounded by a distinct polymeric membrane, whereas nanospheres are matrix-type systems where the drug is uniformly distributed throughout the polymer matrix [90]. The ability to protect drugs and other molecules exhibiting biological activity from the external environment and that to improve their therapeutic index and bioavailability are all advantages of employing PNPs as drug delivery systems [80]. In comparison with other types of nanoparticles, PNPs have received more attention for the management of RB [91].

Doxorubicin (DOX)-loaded poly-B-hydroxybutyrate microspheres

Microspheres are monolithic particles with a biodegradable polymer matrix that can be porous or solid. Owing to their pore interconnectivity, low mass density, and large surface area, they are of biotechnological interest where they can provide good particle size control. Polymeric microspheres produced from natural and synthetic polymers may be suitable as monolith templates. They provide a vital role as scaffolds for targeted distribution of bioactive chemicals in a controlled way to improve ocular drug delivery [92]. Regarding RB, DOX-loaded poly-B-hydroxybutyrate microspheres showed extended DOX diffusion to the posterior segment of the eyes, enhancing

Table 3 Advantages of NLCs compared to SLNs limitations regarding ocular drug delivery

Advantages of NLCs	Disadvantages of SLNs
Superior encapsulation efficiency Excellent ocular permeability Proper pharmacokinetic characteristics Extended and controlled drug release Maintaining adequate drugs' concentrations within the aqueous humor, vitreous humor, and retina -Increasing pre-corneal drug retention Increasing drugs' corneal permeation Increasing ocular bioavailability and distribution Positively-charged NLCs have shown to promote a prolonged ocular residence time, circumventing ocular toxicity owing to their close contact with negatively charged mucus membrane Superior biocompatibility and stability	Initial burst release of SLNs Low drug loading efficiency SLNs for ocular drug delivery have not recently assessed through extensive clinical trials, and most investigations have only undergone *in-vitro* evaluations Retinal cell toxicity of SLNs has not been thoroughly studied till current date

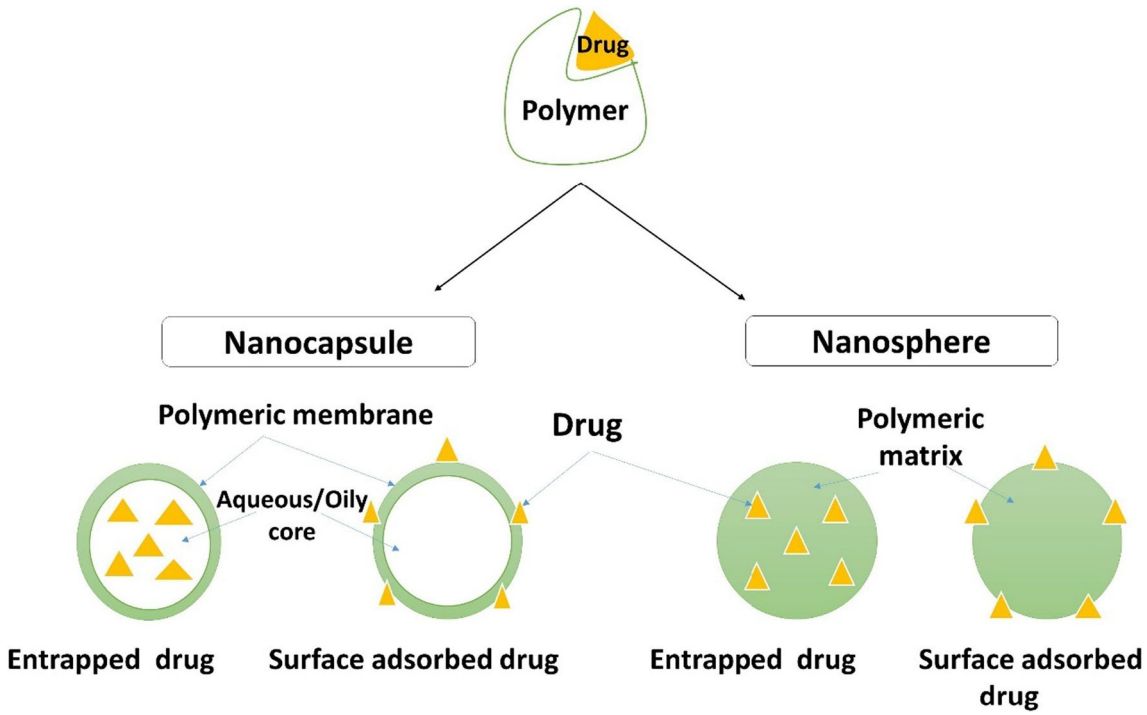

Fig. 4 Representation of polymeric-drug delivery systems; nanocapsules and nanospheres

the drug's penetration into retinal tissues as compared to DOX suspension drops [93].

Carboplatin hyper-branched PAMAM dendritic nanoparticles

Hyper-branched poly(amidoamine) (PAMAM) dendrimers are a novel three-dimensional architecture with nanoscale size and cationic surface charge that could be used as siRNA condensing agents in addition to sturdy nanovectors for targeted ocular drug delivery [71]. Kang et al. [94] proved that carboplatin loaded on dendrimer type PAMAM resulted in an increase in carboplatin's bioavailability which lessened tumor mass in RB. Carboplatin-loaded dendrimers were retained in the tumor vasculature for a longer duration of time and penetrated the sclera until reaching the contralateral eye via the local vasculature, resulting in a prolonged therapeutic effect compared to free carboplatin. Meanwhile, Makky et al. [95] proved an enhanced targeting and reduced toxicity outcomes when loading concanavalin on porphyrin glycodendrimers used in photodynamic therapy for the management of intraocular cancers and RB.

Chitosan nanoparticles

Chitosan is a natural biodegradable polymer that has been extensively researched due to its significant mucoadhesive properties. The ionic interactions provided by chitosan's positively charged nature with the anionic ocular mucosa improve the drug's mucoadhesion, permeability, and retention time on the ocular surface. Consequently, chitosan-based nanoparticulate systems can reduce the number of ocular injections needed while increasing long-term patient compliance [96]. In a previous study, chitosan nanoparticles were fabricated with the goal of delivering DOX to the Y79 RB cell line with increased folate receptor concentration, in which they proved their superior cytotoxicity compared with their unmodified counterparts [97]. Another study demonstrated the augmented efficacy of thiolated chitosan nanoparticles comprising topotecan relative to free topotecan in Y79 RB cells [98]. Moreover, Delrish et al. [99] demonstrated increased ocular bioavailability of thiolated chitosan carboxymethyl dextran nanoparticles in retinoblastoma induced rat eyes. Additionally, Godse et al. [100] revealed that galactose conjugated chitosan nanoparticles loaded with etoposide exhibited greater cytotoxicity and resulted in higher apoptosis in RB Y-79 cells relative to pure etoposide. Furthermore, a previously performed *in-vivo* study showed that lauric acid-grafted chitosan-alginate nanoparticles incorporating melphalan enhanced its penetrability to the vitreous cavity with augmented efficacy, delineating their potential for RB treatment [101].

Another study reported the formulation of a micellar system based on the hydrophilic poly(ethylene glycol) (PEG) and the biodegradable polymer PLGA comprising DOX, in which folic acid was added to the outer surface of PLGA-PEG-PLGA micelles in order to target the highly expressed folate receptor in Y79 RB cells. This delivery system showed a two-week prolonged release of DOX and a four-fold increase in cell absorption relative to the free drug [102]. A recent study reported the design of curcumin and nutlin-3a loaded folate-tagged PLGA nanoparticles to antagonize multidrug resistance (MDR) pathways and augment tumor cell death. The combined action of curcumin and nutlin-3a expanded therapeutic efficacy for RB treatment [103]. Also, Rebibo et al. [104] fabricated stable and non-irritant PLGA nanocapsules loaded with tacrolimus (TAC) for RB treatment. These nanocapsules showed superior enhancement in augmenting drug retention and diffusion to posterior eye compartments.

Inorganic NPs

Inorganic nanoparticles, comprising non-carbon-based molecules, have attracted significant attention in ocular drug delivery owing to their capacity to be altered in size, form, and crystallinity, besides their large surface area, high density of surface ligand attachment, and simplicity of functionalization. They are divided into metallic and non-metallic NPs [59]. Mesoporous silica, iron oxide, silver, gold, and cerium oxide NPs are the most common types of these nanoparticles used for the delivery of anticancer drugs in treatment of RB disease [7].

Metallic NPs

Metallic nanoparticles are flexible single-element nanomaterials. Some of the most common nanoparticles include Au, Ag, Pt, Cu, Pd, Re, Zn, Ru, Co, Cd, Al, Ni, and Fe nanoparticles. Owing to their flexibility, they can alter composition, shape, size, assembly, structure, and optical properties [72]. They've received much more attention due to their advanced characteristics, such as high surface energy, optical properties, quantum confinement and plasmon excitation, rendering them potential for ocular drug delivery [7].

Silver NPs (AgNPs)

Silver nanoparticles have been widely used in ocular administration of drugs owing to their distinct physical and chemical properties, large surface area-to-volume ratio, biocompatibility, and low production cost, which render them suitable candidates as drug delivery carriers [105]. Silver NPs were employed in RB treatment owing to their affordability, stability, environmentally friendly manufacturing process, and optical properties. Advanced plasma mass spectroscopic techniques, X-ray diffraction (XRD), high-resolution transmission electron microscopy (HR-TEM), Fourier transform infrared spectrum (FTIR), and UV–visible spectroscopy were employed to investigate the synthesized AgNPs [106]. A previous study reported the cytotoxic efficiency of AgNPs derived from natural sources of brown seaweed Turbinaria ornata against RB cells [107]. Meanwhile, another study reported that AgNPs resulted in cell cycle arrest in G1, and S phases mediated by repression of RB protein phosphorylation using stem mouse embryonic stem cells (mESCs) [108].

Gold NPs (AuNPs)

Gold is a noble metal noted for its peculiar optical characteristics, caused by the well-known phenomena of localized surface plasmon resonance. This effect is greatly affected by its shape and is the primary cause for its capability to penetrate biological tissues [85]. The effectiveness of AuNPs as therapeutic agents has been studied in RB treatment on the account of their large surface areas, which allow the adsorption of various functional agents [86]. Accordingly, gold NPs have been studied as drug carriers in RB owing to their ability to [109]:

(i) Enhance permeability and retention (EPR) of drugs into the tumor's leaky neovessels, promoting their passive targeting capacity to the tumor site.
(ii) Sustain drugs' release in response to internal or external triggering factors.
(iii) Alter the surface with targeting ligands enhancing tumor-selective accumulation as compared to free drugs.
(iv) Increase the solubility and stability of the drug while also providing a high drug loading capacity by the virtue of their large surface area.

Wang et al. [110] proposed using mesoporous gold nanocages (AuNCs) linked with iron oxide (Fe_3O_4) nanoparticles loaded with muramyl dipeptide (MDP), an immunomodulator and perfluoropentane (PFP), a diagnostic imaging for RB diagnostic imaging and treatment. The cytotoxicity of AuNCs-Fe3O4/MDP/PFP in retinal pigment epithelium ARPE-19 cells and RB Y79 cells was verified, indicating that the delivery system was physiologically safe *in-vitro* and *in-vivo*, accelerating its implementation clinically.

Iron oxide NPs

Iron oxide NPs are magnetic nanoparticles composed of magnetic elements such as iron, cobalt, chromium, and manganese [103]. Since their reactive surface can be modified with biocompatible coatings or bioactive

chemicals, they can form a robust drug delivery system that increases their selectivity toward biological targets while avoiding interaction with healthy cells [104]. Iron-containing magnetic nanoparticles combined with heat were employed for the treatment of RB. Hyperthermia is a powerful cancer treatment method because tumor cells are more heat sensitive compared to healthy cells. The temperature may be raised using a variety of techniques, such as microwaves, radio frequency, and focused ultrasound. Iron nanoparticles have been employed as nanoheaters that can target tumor cells without harming healthy tissues [111].

Demirci et al. [111] evaluated magnetic hyperthermia in the Y79 RB cell line utilizing dextran-coated iron nanoparticles. The results indicated that following 24 h of magnetic hyperthermia therapy, apoptosis in 46% to 73% of Y79 RB cells was denoted, suggesting the functionality of magnetic hyperthermia employing dextran-coated iron nanoparticles as an effective therapeutic approach for RB.

Mesoporous silica NPs (MSNPs)

Mesoporous silica nanoparticles are among the most extensively researched inorganic nanoparticles in ocular drug delivery. MSNPs are biodegradable nanomaterials that have the potential to break down into silica or silicic acid. Owing to their known biocompatible nature, they represent one of the most propitious substrates for biological applications including drug administration [7]. It has been determined that MSNPs may increase the solubility and bioavailability of lipophilic molecules due to the subsequent merits [112, 113]:

(i) MSNPs' surface is hydrophilic, which improves their wettability. Additionally, the hollowness, surface chemistry, and pore size of microspheres may change the rate of drugs release from them.
(ii) Enhancement of the amount of entrapped drugs owing to MSNPs' lack of crystallinity.
(iii) Large surface area and high dispersibility.

It was reported that functionalized mesoporous nanoparticles loaded with camptothecin (CPT), an anticancer agent, as well as one or two photon excitation photosensitizers for photodynamic therapy (OPE-PDT and TPE-PDT) showed their effectiveness using Y79 cells in treating RB [114]. Furthermore, Qu et al. [115] demonstrated that carboplatin (CRB) loaded MSNPs increased cancer cell death in RB cells relative to free CRB. Additionally, Gary-Bobo et al. [116] developed a one-photon excitation photodynamic therapy agent (OPEPDT) employing CPT, mannose, or galactose in MSNPs to target Y-79 RB cells which showed a propitious therapeutic synergy for destroying RB cells. Meanwhile, Warther et al. [117] reported the efficacy of mannose-functionalized MSNPs for targeting and imaging RB cells. MSNPs were almost always located in lysosomes, suggesting that they invade cells via an endocytic pathway.

Cerium oxide NPs (CeONPs)

Cerium represents the first element in the lanthanide group and appears in both the CeO_2 and $Ce2O_3$ oxidation states. Cerium oxide nanoparticles have cerium (III) and cerium (IV) on their surface, and the pharmacological activity of these nanoparticles depends on their capacity for oxygen absorption and release [118].

Cerium oxide NPs (CeONPs), which have anti-inflammatory and antioxidant characteristics, have attracted a lot of attention in nanotechnology [119]. CeONPs are a viable alternative therapy for a range of acute and chronic disorders since ROS-induced oxidative stress is linked to several disorders [120]. In a previous study, CeONPs showed inhibition in the apoptotic signaling pathway of RB Y78 cell lines, increasing genes expression accompanied by neuroprotection, and decreasing the ROS [119]. Furthermore, Gao et al. [121] reported a novel nanocarrier composed of glycolic chitosan-coated cerium nanoparticles (GCCNP) as a pH-sensitive controlled drug delivery system that can deliver doxorubicin (DOX) for pH-sensitive and tumor-targeted combination therapy. This study reported a synergistic approach for improving the therapeutic potential and lowering the adverse effects of DOX with significant reduction of tumor growth, in addition to improving the *in-vivo* biocompatibility of the proposed NPs with healthy retinal cells. Additionally, Kartha et al. [122] demonstrated the efficacy of cerium-doped titanium dioxide nanoparticles (Ce-doped TiO_2) for their anticancer effects against Y79 RB tumor cells compared to TiO_2 nanoparticles. Both nanoparticles were incubated in Y79 RB cancer cells and then treated with UV irradiation for various time periods varying from one to six hours. Ce-doped TiO_2 showed augmented anticancer cytotoxicity compared to TiO_2 nanoparticles owing to the ability of cerium element to retain the integrity of DNA, generally lost in cancerous cells, by acting on the intimate pathways governing the survival of cancerous cells.

Multifunctionalized nanocarriers

Multifunctional NPs are advanced nanoparticulate systems which can deliver one or more therapeutic compounds, enabling biomolecular targeting through one or more conjugated antibodies or other ligands, and magnifying imaging signals by encapsulating contrast agents [65, 123].

Surface-modified melphalan NPs for the intravitreal chemotherapy of RB

Compared to unmodified NPs, surface-modified melphalan NPs exploited superior effectiveness against RB cells, in which they demonstrated higher efficacy compared to other NPs [124]. Future studies are required to demonstrate the capacity of these nanoparticles to enhance drug's transport to the vitreous humor, where it is expected that surface modification will have a bigger influence on efficacy.

Galactose-functionalized nanocarriers

The sugar entities ligand-based mechanistic technique for attaining enhanced and customized RB treatment is in great demand. RB cells express considerably more sugar moieties in the form of lectins than healthy cells. Hence, targeting overexpressed lectins is an effective way for achieving successful results [125].

Human RB cells express sugar receptors (lectins) with a preference for galactose and mannose residues, according to a prior work by Godse et al. [125]. Sugar is therefore a desirable ligand that can be used to target and improve the endocytosis of drugs-loaded NPs. Additionally, unlike folic acid, sugars do not have photosensitivity or stability concerns. The authors observed that etoposide loaded PLGA nanoparticles coated with chitosan and galactose for treatment of RB slowed the drug release rate and helped in the active targeting of RB cells. Also, cytotoxicity and apoptosis experiments demonstrated that these NPs had improved the drug's cellular internalization, promoting superior anti-cancer activity.

Hyaluronic acid (HA)-functionalized nanocarriers

HA is an FDA-approved marine polymer possessing exceptional biodegradability, flexibility, mobility and shielding, in addition to an anticancer action on the HA receptor, the CD44 receptor. A previous study reported that the formulation of electrostatically coated nanoparticles incorporating nonverbal polymeric gene DNA complexed with HA provided increased intravitreal drug delivery in RB cells [126].

Folic acid (FA)-functionalized nanocarriers

Coupling nanocarriers with a targeting moiety can be more successful compared to systemic chemotherapy in the targeted eradication of tumor cells [103] Targeted molecules allow spatial delivery of antitumor agents [98]. Folate receptors are highly expressed in RB cells, so exploiting them in RB treatment to selectively uptake NPs and only kill cancer cells will be very effective [127]. In a study reported by Mitra et al. [128], CNPs and DOX conjugated with folic acid proved their efficacy for targeting RB cells.

Conclusions and future prospects

Retinoblastoma is a type of challenging pediatric ocular cancer that is difficult to treat by the conventional approaches owing to drug expulsion and non-targeted delivery, resulting in therapeutic inefficiency. Nanoparticles-mediated antitumor drug delivery proved to increase therapeutic potential, lower toxicity, customize site-specific delivery and ligand binding that may transport drug through several routes of administration, hence causing cost-effectiveness and cytotoxicity management of RB. These delivery systems have shown their effectiveness to lower the barriers to treating RB and prevent the loss of normal cells. Emerging advances in multifunctionalization and biocompatible ligands in anticancer therapy and diagnosis are ushering in a new era of surpassing conventional barriers by strategically enhancing RB treatment and diagnosis. With the revolutionary breakthrough of nanomedicine in cancer diagnosis, experimental research is designed to establish cell/tissue-specific nanosystems to suit the demanding criteria of intraocular chemotherapy and diagnostics. The last frontier in this study is employing "intelligent nanosystems with several functions" (i.e., systems capable of reaching the challenging anatomical eye components affected by RB). However, further pre-clinical research is required before evaluating the method in clinical trials to determine its benefit-to-risk ratio.

Abbreviations

AgNPs	Silver nanoparticles
AuNPs	Gold nanoparticles
BRB	Blood retinal barriers
CD44	Cluster of differentiation 44
CeONPs	Cerium oxide nanoparticles
CH	Chitosan
CNPs	Chitosan NPs
COG	Children's Oncology Group
CSF	Cerebrospinal fluid
DCM	Dichloromethane
DOX	Doxorubicin
EDTA	Ethylenediamine tetra-acetic acid
FA	Folic acid
Fe_3O_4	Iron oxide
FITC	Fluorescein isothiocyanate
HA	Hyaluronic acid
HTS	High-throughput screening
IIRC	International classification of intraocular retinoblastoma
IVi	Intravitreous chemotherapy
LNP	Lactoferrin nanoparticle
LNPs	Lipid nanoparticles
MDP	Muramyl dipeptide
MRI	Magnetic resonance imaging
MDR	Multidrug resistance
MSNPs	Mesoporous silica nanoparticles
NLCs	Nanostructured lipid carriers
NPs	Nanoparticles

OAC	Ophthalmic artery chemosurgery
PCL	Poly-caprolactone
PFP	Per fluoro pentane
PLGA	Poly-D, L-lactic-*co*-glycolic acid
PMMA	Polymethylmethacrylate
RB	Retinoblastoma
ROS	Reactive oxygen species
SCS	Suprachoroidal space

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Declarations

Ethics approval and consent to participate
This article does not include any studies involving human or animal subjects.

Consent for publication
This article does not contain any studies involving human subjects.

Studies involving plants
This article does not contain any studies involving plants.

Competing interests
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