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Therapeutic Potential of Phytochemicals in Retinoblastoma: Comprehensive Review

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Abstract

Background: Retinoblastoma is the most common primary intraocular malignancy in children and is primarily caused by biallelic inactivation of the RB1 tumour suppressor gene, leading to dysregulation of the cell cycle. Despite advances in multimodal treatment approaches such as systemic and intra-arterial chemotherapy, focal therapies, radiotherapy, and enucleation, current treatment strategies remain limited due to significant systemic and ocular toxicities, chemoresistance, and suboptimal eye and vision preservation, particularly in resource-limited settings. **Aim:** The present review aims to evaluate the therapeutic potential of phytoconstituents in the management of retinoblastoma and to highlight their role as safer, multi-target anticancer agents in paediatric ocular oncology. **Methods:** Literature search was conducted using various databases like PubMed, Google Scholar and Web of Science with keywords like retinoblastoma, RB1, genetics, signalling pathways and phytochemicals having anticancer properties. **Discussion:** Phytochemicals play an anticancer role in retinoblastoma through various signalling pathways like NF-κB, CDK, JAK/STAT MAPK/ERK and PI3K/AKT/mTOR. The phytochemicals show various activities like pro-apoptotic, anti-angiogenic and anti-invasive properties. **Conclusion:** Phytoconstituents represent promising adjuncts or alternatives to conventional retinoblastoma therapies. However, further preclinical and clinical investigations are required to overcome formulation challenges such as ocular barriers and poor solubility, and to translate these natural compounds into effective therapeutic strategies.

Major Finding: Phytochemicals show promise in retinoblastoma by targeting multiple oncogenic pathways with low toxicity, making them potential candidates for drug development. Their ability to induce apoptosis, inhibit tumour progression, and enhance therapeutic efficacy further supports their potential as safer, more effective alternatives for retinoblastoma management.

Keywords: Genetics, Molecular Pathology, Pathways, Phytochemicals, Retinoblastoma, Toxicities

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1. Introduction

Retinoblastoma is the most common primary intraocular malignancy, which occurs in children before the age of 5 years, with an approximate incidence of 1 case in 15,000-20,000 live births worldwide[1,2]. Survival rate exceeds 90% in high-resource environments, while it is much lower in many lower and middle-income countries due to late diagnosis and limited access to specialised care[3]. The disease results from biallelic loss of function of the RB1 gene at chromosome 13q14, which encodes a critical regulator of the G1-S cell cycle checkpoint. Germline RB1 mutations underline heritable, often bilateral disease in approximately one-third of patients, while non-germline RB1 alterations typically give rise to unilateral tumours[4].

Current management, aimed at maximising survival while preserving the globe and useful vision, consists of combinations of systemic and intra-arterial chemotherapy, intravitreal chemotherapy, focal therapies (laser photocoagulation, thermotherapy, cryotherapy), radiotherapy and enucleation for advanced eyes[5]. However, even while these have elevated survival in high resource settings above 90%, they are still bound by systemic toxicities, myelosuppression, ototoxicity and nephrotoxicity, ocular complications such as retinal

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ischemia, vascular occlusion and radiation-induced damage, chemoresistance, incomplete vision salvage and survivors are at an increased risk of developing second primary malignancies in the heritable form[6].

Current retinoblastoma treatment relies on chemotherapy, focal therapies, radiotherapy, and enucleation, which are often invasive and cytotoxic[7]. Although these approaches improve survival, they are associated with significant systemic and ocular toxicities and limited visual preservation. Treatment resistance and the risk of secondary malignancies, particularly in heritable disease, remain major concerns[8]. Phytochemicals offer multitargeted anticancer activity with comparatively favourable safety profiles. Their ability to modulate oncogenic pathways while providing retinal protection supports their potential as safer adjunct or alternative therapies[9].

Phytochemicals, including flavonoids, alkaloids, terpenoids and phenolic acids, exhibit wide anticancer activities by displaying antioxidant effects, modulating oncogenic signalling, inducing apoptosis and cell cycle arrest and inhibiting angiogenesis and metastasis, which make phytochemicals attractive candidates targeting the complex molecular network driving retinoblastoma[10]. Indeed, many plant-derived compounds used in oncology, such as epipodophyllotoxins, taxanes, vinca alkaloids and camptothecin derivatives already illustrate that natural products can yield clinically effective, and mechanism-based anticancer agents[11].

Additionally, numerous plant-derived constituents, such as curcumin, quercetin, catechins, saffron, carotenoids and Ginkgo biloba extracts have demonstrated the potential for antioxidant, anti-inflammatory and neuroprotective effects, supporting

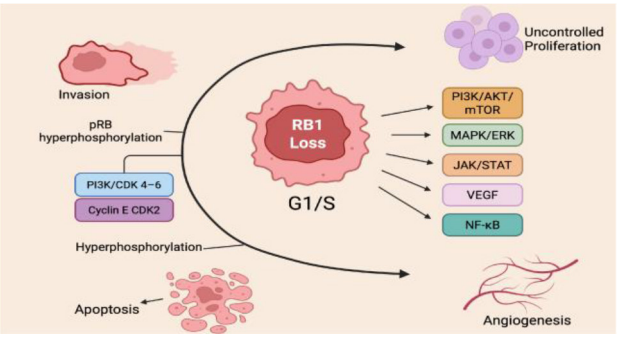


Figure 1. Diagrammatic representation of cell cycle dysregulation induced by loss of the RB1 gene in retinoblastoma.

their possible utility in protecting retinal tissue and modulating the tumour microenvironment in ocular diseases[12].

1.1 Molecular Pathology and Therapeutic Targets in RB

Loss of RB1 function, coupled with dysregulation of multiple oncogenic signalling pathways, drives uncontrolled proliferation, survival, and dissemination in retinoblastoma. Notably, these aberrant pathways also represent convergent therapeutic targets for phytochemicals, which exhibit pro-apoptotic, antiproliferative, anti-angiogenic, and anti-invasive activities[13]. Biallelic inactivation of RB1 completely abolishes pRB-mediated control of the G1-S checkpoint, releasing E2F transcription factors and allowing unrestricted expression of S-phase genes[14]. Upstream, the cyclin D/CDK4-6 and cyclin E/CDK2 complexes hyperphosphorylate and inactivate pRB so that overactivated CDKs further amplify cell cycle progression in RB[15].

RB tumours often engage in survival and growth signalling through PI3K/AKT/mTOR, MAPK/ERK and JAK/STAT cascades by promoting proliferation, metabolic support and resistance to apoptosis[16]. There is also enhanced NF-B signalling that drives the transcription of genes promoting inflammation, survival, invasion and therapy resistance[17]. In parallel, angiogenesis and metastatic potential are enhanced through upregulation of VEGF and related pro-angiogenic factors, remodelling of extracellular matrix components and epithelial-mesenchymal transition-like changes that enable local invasion and extracellular spread. These alterations cumulatively establish a molecular profile typified by aggressive tumour growth, resistance to cell death and a high propensity for metastasis[18].

Phytoconstituents frequently target multiple signalling nodes; they can simultaneously counter CDK- driven proliferation and survival pathways downstream of RB1 loss by inhibiting CDK activity or restoring cell cycle checkpoints and inducing G1/S arrest[19]. Various plant-derived agents have been demonstrated in cancer models to inhibit PI3K/AKT/mTOR, MAPK/ERK, JAK/STAT and NF-B signalling thereby reducing proliferation, sensitising cells to apoptosis and downregulating anti-apoptotic

proteins[20]. RB1 loss causes aberrant G1/S transition, pRB hyperphosphorylation, and activation of key proliferative and angiogenic pathways, driving retinoblastoma progression as shown in Figure 1.

Phytochemicals also act through anti-angiogenic and anti-invasive effects by reducing the expression of VEGF/VEGFR, interfering with downstream angiogenic signalling, and modulating matrix-degrading enzymes and EMT-related transcription factors[21]. In the context of retinoblastoma, this multi-target profile makes phytochemicals promising candidates to complement existing therapies aimed at the inhibition of tumour growth, induction of apoptosis and limitation of neovascularisation and metastatic spread by convergent blockade of these dysregulated pathways[22].

2. Materials and Methods

An exhaustive literature search was carried out using online databases such as PubMed, Scopus, ScienceDirect and Google Scholar. The search strategy involved the use of keywords such as RB1 gene, ocular drug delivery system, gene therapy, molecular pathogenesis, immunotherapy, retinoblastoma, clinical trials and nanoparticles. The literature search was limited to peer-reviewed review articles published in English between 2020 and 2025. Studies were selected based on their relevance to retinoblastoma, covering its biological basis, molecular mechanisms, diagnostic biomarkers and evolving therapeutic strategies with a focus on advanced drug delivery systems and immunotherapeutic interventions. Non-peer-reviewed articles, conference abstracts, and duplicate articles were not included in studies.

2.1 Overview of Phytoconstituents and Natural Derivatives

Phytoconstituents relevant to retinoblastoma are classified into the following four broad classes: polyphenols, alkaloids, terpenoids and other plant-derived molecules (saponins, lignans, polysaccharides and complex extracts).

2.1.1 Polyphenols

Polyphenols are a major family of plant secondary metabolites that contain one or more aromatic rings with multiple hydroxy groups[23]. The major classes of polyphenols comprise flavonoids, stilbenes and curcuminoids, which are commonly found in fruits, vegetables, tea and spices. In cancer models, the potent anti-cancer activities of polyphenols involve the scavenging of reactive oxygen species and the regulation of various redox-dependent signalling pathways, which result in the inhibition of the cell cycle at the G0/G1 or G2/M phases by interfering with CDKs, cyclins, and regulatory proteins, including p21 and p27[24]. Polyphenols initiate the intrinsic and extrinsic apoptotic pathways by inducing mitochondrial dysfunction, activating various caspases and reducing the expression of anti-apoptotic members of the Bcl-2 family[25]. Moreover, such compounds inhibit key oncogenic signalling cascades, including PI3K/AKT/mTOR, MAPK/ERK, JAK/STAT, and NF-κB, accounting for strong antiproliferative and chemosensitising effects. They also suppress angiogenesis and tumour invasion by downregulating VEGF/VEGFR, reducing the activity of MMP-2 and MMP-9 and inhibiting epithelial-mesenchymal transition (EMT) markers[26].

2.1.2 Terpenoids

Terpenoids are the isoprenoids that comprise monoterpene, sesquiterpene, diterpene, triterpene, and their oxygenated derivatives. Various examples with anticancer potentials are sesquiterpene lactones (xanthatin, parthenolide), sesquiterpenes like β-elemene, and triterpenes like ursolic, oleanolic, and betulinic acids[27]. In cancer studies, terpenoids generally trigger apoptosis via mitochondrial depolarisation, production of reactive oxygen species and activation of caspases. Terpenoids may also trigger cell cycle arrest via the regulation of CDKs and cyclins. Terpenoids also inhibit key cell survival and inflammatory pathways such as NF-kB, STAT3, PI3K/AKT, and, in some instances, MAPK, leading to a reduction of tumour cell proliferation and resistance[28]. They also have strong anti-angiogenic and anti-metastatic effects through downregulation of VEGF, HIF-1α, invasion-related proteins like MMPs, and adhesion molecules, leading ultimately to restriction of tumour growth, vascularisation, and spread[29].

2.1.3 Alkaloids

Alkaloids are a group of heterocyclic compounds with pharmacological activity and contain nitrogen in their

structure. Traditional medicines such as vincristine, vinblastine, a derivative of podophyllotoxin named etoposide and camptothecin derivatives have been developed from this class, reflecting their potential for translation to human medicine. In cancer biology, alkaloids such as berberine, matrine, neferine, and indoles/isoquinolines have been shown to exert their antitumor effect through inhibition of cancer cell proliferation by inducing G0/G1 or G2/M arrest in the cell cycle through modulation of CDKs, cyclins, and p53/p21 signalling pathways[30]. These compounds also induce apoptosis through the mitochondrial pathway, which is associated with downregulation of anti-apoptotic proteins such as Bcl-2, Bcl-xL and upregulation of pro-apoptotic proteins such as Bax and activated caspases. In addition, alkaloids have been shown to downregulate key survival and inflammatory signalling pathways such as PI3K/Akt, MAPK/ERK, and NF-κ. Further, they reduce invasion and metastasis by the downregulation of MMP-2, MMP-9, uPA, and EMT-associated transcription factors, thus ultimately dampening the aggressive behaviour of cancer cells[31].

2.1.4 Other Classes and Complex Plant Extracts

Other classes of substances from plants include polysaccharides from Astragalus, which can affect immune system activity, decrease the invasion of tumour cells and modify the extracellular matrix with little or no direct cell killing activity[32]. Antioxidant, anti-proliferative and anti-angiogenic properties of Lignans and Coumarins are attributed to the modulation of some hormone and redox-sensitive pathways. Saponins and glycosides have membrane activity, are pro-apoptotic and have chemosensitising effects, which may increase the effectiveness of standard chemotherapy[33]. Complex extracts sourced from milk thistle, ginger, lotus, Pueraria and Astragalus contain diverse mixtures of polyphenols, terpenoids and alkaloids which collectively exhibit antiproliferative, pro-apoptotic, and anti-angiogenic. and anti-invasive activities *in vitro*, including models relevant to retinoblastoma[34]. Key plant-derived extracts and their mechanistic actions against RB-related pathways are summarised in Table 1.

2.2 Formulation and Delivery Aspects

Phytochemicals, despite their promising anticancer properties, face a host of profound physicochemical barriers that seriously impede the therapeutic delivery to intraocular retinoblastoma tumours. The principal drawback is their inherently poor aqueous solubility. Most polyphenols such as curcumin (~ 0.4 μg/mL, pH 7.4), flavonoids, including quercetin (~2 μg/mL), terpenoids represented by β-elemene (<1 μg/mL) and alkaloids like berberine (~5 μg/mL), exhibit log P values greater than 3-6, making them practically insoluble in physiological fluids such as vitreous humor or tear film[52,53]. Low aqueous solubility precludes adequate dissolution and diffusion through biological barriers, causing precipitation of the drug *in situ*, leading to incomplete drug release under perfect sink conditions-a condition where the volume of the medium maintains drug concentration below 10-30% of saturation solubility-resulting in bioavailability, often less than 1-5% on oral or systemic administration[54,55].

This is compounded by rapid and extensive metabolism, primarily via hepatic cytochrome P450 enzymes (CYP3A4/2C9 oxidation) and phase II conjugation (glucuronidation/sulfation by UGTs/SULTs) coupled with intestinal and ocular efflux by ATP-binding cassette transporters such as P-glycoprotein (P-gp), Breast Cancer Resistance Protein (BCRP) and multidrug resistance-associated proteins (MRP1/2)[56]. Phytochemicals given suffer extensive first-pass effects, and plasma half-lives are usually <1-2 h, with peak concentrations rarely exceeding 1-10 ng/mL, well below the micromolar levels necessary to induce cytotoxicity against retinoblastoma cells. Chemical instability further exacerbates the problem, such as polyphenols auto-oxidise into reactive quinones, hydrolyse in a narrow pH range of optimal stability between pH 4 and 6 and photodegrade in ambient light, while terpenoids isomerise and alkaloids protonate/deprotonate in a highly variable manner, yielding degradation half-lives of 30 min to 4 h in simulated vitreous or plasma[57,58].

Ocular anatomy creates static and dynamic barriers that collectively limit phytochemical access to posterior segment tumours. The corneal epithelium is a lipophilic barrier to hydrophilic or large (>500 Da) molecules due to tight junctions and lipid-protein matrices, allowing only ~1-5% transcorneal flux for most phytoconstituents; the conjunctiva and sclera provide alternative paracellular pathways but are subject to rapid vascular/lymphatic presystemic elimination (~80-90% loss)[59]. The posterior segment Blood-Retinal

Table 1. Mechanism of action, biological effects and key findings of plant-derived bioactives targeting key molecular pathways in retinoblastoma

Class	Representative compound	Plant source	Mechanism of action in retinoblastoma	Biological effects in retinoblastoma	Key findings in retinoblastoma
Curcuminoid	Curcumin	*Curcuma longa*	Inhibits CDK activity- G1/S arrest, suppresses survival signaling (PI3K/AKT, NF-κB)	G1/S arrest; modulation of CDKs and p21, inhibition of PI3K/AKT/mTOR, JAK/STAT and NF-κB, anti-angiogenic and anti-invasive (↓VEGF, ↓MMP-2/9, EMT markers)	G1/S arrest, apoptosis, ↓VEGF and ↓MMP-2/9 [35]
Flavonoid	Luteolin	*Ocimum sanctum*,	Inhibits transcription factors regulating proliferation and angiogenesis	Inhibits proliferation, promotes intrinsic apoptosis, blocks STAT3 and NF-κB, anti-angiogenic via VEGF/ VEGFR inhibition	↓Proliferation, apoptosis and anti-angiogenic[36]
Flavonoid	Fisetin	Strawberries, apples	Suppresses survival signalling, induces apoptotic pathways	Induces apoptosis and cell-cycle arrest, suppresses PI3K/AKT and NF-κB signalling, and reduces invasion and migration	Apoptosis, ↓invasion and migration[37]
Phenolic acid	Chlorogenic acid	*Lonicera japonica,* Coffee	Modulates oxidative stress and proliferation pathways	Antioxidant, pro-apoptotic and antiproliferative modulation of PI3K/ AKT and MAPK potential anti-angiogenic effects	Antioxidant, antiproliferative[38]
Flavonoid	Quercetin	Onion, apple	Blocks proliferation pathways, inhibits VEGF and MMPs	Antiproliferative G1 arrest via CDK/cyclin modulation, inhibition of PI3K/AKT and MAPK/ERK, pro-apoptotic and anti-angiogenic (↓VEGF, ↓MMP-2/9)	G1 arrest, ↓angiogenesis[39]
Triterpene	Ursolic acid	*Ocimum*, apple peel	Downregulates inflammatory and hypoxia pathways	Induces apoptosis and cell-cycle arrest, down-regulates NF-κB and STAT3, anti-angiogenic via VEGF/HIF-1α suppression	Apoptosis, ↓angiogenesis[40]
Sesquiterpene	β-Elemene	*Curcuma wenyujin*	Suppresses survival and invasion signalling	Antiproliferative, promotes apoptosis, inhibits PI3K/AKT and NF-κB, reduces invasion and angiogenic signalling	↓Proliferation, apoptosis[41]
Sesquiterpene lactone	Xanthatin	*Xanthium strumarium*	Inhibits mitotic kinase-mitotic arrest (G2/M)	Selective cytotoxicity in RB cells, inhibits PLK1(Polo like kinase 1), leading to mitotic catastrophe, induces apoptosis and G2/M arrest	Mitotic arrest, apoptosis[42]
Triterpene	Betulinic acid	Birch bark	Activates intrinsic apoptosis pathway	Preferentially toxic to tumor cells, triggers mitochondrial apoptosis, inhibits angiogenesis and metastasis-related factors	Tumour-selective apoptosis[43]
Bisbenzyli soquinoline	Neferine	Lotus (*Nelumbo nucifera*)	Modulates survival and stress pathways	Pro-apoptotic, cell-cycle arrest, modulation of PI3K/AKT and MAPK pathways, anti-invasive effects	Apoptosis, ↓invasion[44]
Indole alkaloid	Apparicine	*Taberna emontana*	Disrupts survival signalling PI3K/AKT, induces mitochondrial apoptosis, interferes with cell-cycle progression	Cytotoxic to RB and other cancer cells, induces apoptosis and cell-cycle arrest, interferes with survival signaling.	Cytotoxic, apoptosis [45]

Table 1. Continued...

Class	Representative compound	Plant source	Mechanism of action in retinoblastoma	Biological effects in retinoblastoma	Key findings in retinoblastoma
Isoquinoline alkaloid	Berberine	*Berberis vulgaris*	Induces G0/G1 arrest, inhibits proliferative signaling	G0/G1 arrest via CDK/cyclin modulation, intrinsic apoptosis, inhibition of PI3K/AKT and MAPK/ERK suppression of NF-κB and MMP-2/9	G0/G1 arrest, ↓MMP-2/9 [46]
Quinazoline	Matrine	*Sophora flavescens*	Inhibits inflammatory signaling, induces autophagy	Antiproliferative, induces apoptosis and autophagy, down-regulates NF-κB and STAT, reduces invasion and EMT	Apoptosis, ↓EMT[47]
Mixed polyphenol/terpenoid extract	Ginger, lotus, Pueraria extracts	Multiple plants	Modulate oxidative stress, inhibit PI3K/AKT and NF-κB signaling and suppress angiogenic (VEGF) and invasive (MMPs) pathways	Induce apoptosis and cell-cycle arrest, reduce oxidative stress, inhibit angiogenic and invasive signalling in various tumour models, some data in ocular cells and RB lines	Apoptosis, ↓angiogenesis[48]
Polysaccharide	Astragalus polysaccharides	*Astragalus membranaceus*	Enhance immune response (macrophages, T-cells), downregulate MMP expression; suppress inflammatory signalling	Immunomodulatory, anti-invasive via reduced MMP expression, may enhance host antitumor immunity and limit metastasis	Immuno modulatory, ↓metastasis[49]
Complex flavonolignan mixture	Milk thistle (silymarin/silybin)	*Silybum marianum*	Antioxidant activity, inhibits NF-κB/MAPK signalling, and modulates apoptotic proteins (↑Bax, ↓Bcl-2)	Antioxidant and hepatoprotective, antiproliferative and pro-apoptotic in several cancer models, potential to protect normal tissues and modulate drug toxicity	Apoptosis, cytoprotection[50]
Saponin-rich extract	Ginsenoside-containing ginseng extract	*Panax ginseng*	Inhibits PI3K/AKT and NF-κB signalling, modulates apoptotic proteins (↑Bax, ↓Bcl-2) and enhances chemosensitivity, suppresses VEGF-mediated angiogenesis	Pro-apoptotic; chemosensitizing, inhibition of PI3K/AKT and NF-κB, anti-angiogenic	Apoptosis, chemo sensitization[51]

Barrier (BRB) consists of tight junctions between the retinal pigment epithelium and choroidal endothelium and actively excludes xenobiotics via P-gp/MRP1 efflux, like the blood-brain barrier[60]. High choroidal blood flow (~700 mL/min total ocular) and vitreous convection (anterior outflow ~1-3 µL/min; posterior, diffusion-limited) dilute and clear intravitreal doses; free drug vitreous half-lives of 20-40 h are further reduced by enzymatic degradation. Retinoblastoma tumours in the posterior pole or the vitreous seeds thus result in subtherapeutic exposure since systemic dosing produces intraocular concentration <0.1% of plasma levels[61].

Systemic administration to achieve tumoricidal intraocular levels amplifies toxicity risks, especially in pediatric patients. High doses elicit gastrointestinal irritation, hepatotoxicity (elevated ALT/AST via oxidative stress), nephrotoxicity and possible cardiotoxicity, while pharmacokinetic interactions such as CYP3A4 inhibition/induction affect co-administered chemotherapeutics in retinoblastoma, like vincristine, *i.e.*, increasing myelosuppression or

carboplatin altering its nephrotoxicity[62]. Immature drug-metabolising enzymes in paediatrics increase susceptibility, while chronic dosing for adjuvant or chemopreventive purposes increases the risks of secondary malignancies in germline RB1 carriers[63]. Altogether, these challenges of poor sink-compliant solubility, metabolic lability, impenetrable ocular barriers, and poor safety profiles mandate advanced formulations to enable clinically viable phytochemical delivery for the treatment of retinoblastoma[64].

Current methods to formulate and deliver phytochemicals have been aimed towards overcoming the presence of low-water solubility, uncompromised stability and barriers of the ocular area that may prevent sufficient drug levels from reaching the retinoblastoma lesions of the eye with minimal systemic toxicity. Nanocarriers, liposomal/niosomal systems, and polymeric nanoparticles, along with localised intravitreal or periocular administration, are central to these emerging approaches, and several plant-derived agents have already been investigated in relevant ocular or tumour models[65].

2.2.1 Nanocarriers for Phytochemicals

Nanocarriers (typically 50-200 nm) enhance apparent solubility, protect phytochemicals from degradation, and promote tumour uptake through endocytosis, passive targeting, and/or ligand-mediated targeting[66]. Compared with free curcumin, curcumin-loaded polymeric and lipid nanoparticles exhibit higher intracellular accumulation, more potent inhibition of PI3K/AKT and NF-κB signalling, and more robust induction of apoptosis in models of cancer. For ocular tumours, nanoparticle-based delivery systems have been shown to elevate drug levels in retina and choroid several-fold and maintain them for days to weeks following periocular or intravitreal administration, which is critical for sustained control of retinoblastoma[67].

2.2.2 Liposomal and Niosomal Systems

Liposomes are phospholipid vesicles, and noisome are non-ionic surfactant vesicles that encapsulate hydrophobic phytochemicals within their bilayers or aqueous cores. Because of biocompatibility and interaction with ocular surfaces, both liposomes and noisome are well-suited for ocular delivery. Preclinical cancer studies have demonstrated that liposomal curcumin increases aqueous solubility, prolongs circulation time, and enhances tumour accumulation, leading to much stronger tumour growth inhibition compared to unformulated curcumin[68]. Niosomal formulations of flavonoids and alkaloids enhance corneal/scleral permeation and cellular uptake while reducing burst toxicity, which may be advantageous in targeting sensitive intraocular tissues. In ocular models, vesicle-based formulations of antioxidant phytochemicals achieve higher retinal concentration after topical or periocular administration and better preserve retinal structure and function compared with free compounds[69].

2.2.3 Polymeric Nanoparticles and Advanced Polymer Systems

PLGA, PLA, chitosan, or hyaluronic acid-based biodegradable polymeric nanoparticles enable controlled release and, in the case of surface modification, active targeting of phytochemicals to tumour cells. According to the reviews on phytochemical delivery, PLGA nanoparticles loaded with curcumin, quercetin, or berberine reveal enhanced physicochemical stability, sustained release, and higher antitumor efficacy *in vitro* and *in vivo* by more effective suppression of survival pathways and induction of apoptosis[70]. Hyaluronic acid-decorated nanoparticles can bind CD44 on tumour cells, thus enhancing the intracellular uptake of encapsulated natural compounds and antiproliferative and anti-invasive effects. Cationic or mucoadhesive chitosan nanoparticles increase residence time on ocular surfaces and allow improved penetration across corneal and scleral barriers, which is favourable for plant-derived drugs possessing poor intrinsic permeability[71].

2.2.4 Intravitreal and Periocular Delivery Concepts

Local ocular delivery routes represent a critical strategy to attain therapeutic intraocular levels of phytochemicals, with minimal systemic exposure, in children affected by retinoblastoma. Intravitreal injection deposits nanocarrier- or liposome-loaded phytochemicals directly into the vitreous cavity, bypassing the blood-retinal barrier and placing high drug concentrations close to retinal tumors[72]. In animal models, intravitreally injected nanoparticles containing

plant-derived bioactives maintain therapeutic levels in the posterior segment for prolonged periods and reduce injection frequency compared with free solutions. The periocular routes of drug delivery (such as via sub-Tenon's, posterior subconjunctival or via suprachoroidal) can form a depot in proximity to the sclera, thus allowing for localised release of nanocarriers at a slower rate in relation to their diffusion into the retina and choroid, ultimately leading to increased and sustained concentrations of drug within the eye than via systemic administration with concurrent decrease in systemic exposure[73]. Reviews on nanomaterials for medicinal plant extracts emphasise that combining these localised routes with nanocarriers, such as PLGA nanoparticles or solid lipid nanoparticles, besides liposomes, improves the therapeutic index of phytochemicals and supports their investigation as adjuncts in ocular oncology, including retinoblastoma[74]. Table 2 outlines ocular delivery routes used for phytochemical-loaded nanocarriers and their improved posterior segment pharmacokinetics and efficacy.

3. Result and Discussion

3.1 Translational Challenges and Emerging Opportunities

Most phytochemical and plant-derived strategies against retinoblastoma are also still at the preclinical stage, and most of the available evidence is dominated by *in vitro* experiments with only limited *in vivo* work. Translation into clinical use has not yet occurred[86].

3.2 Current Stage of Evidence

Available data on phytoconstituents in retinoblastoma come mainly from cytotoxicity and mechanistic studies in cell lines like Y79, WERI-Rb1, and HXO-RB44, where many plant-derived compounds induce cell-cycle arrest, apoptosis, and inhibition of angiogenic signaling[23]. A small number of studies extend to zebrafish and mouse xenograft models; for example, studies on sesquiterpene lactone xanthatin selectively inhibit growth of retinoblastoma cells *in vitro* and in a zebrafish orthotopic model by targeting polo-like kinase 1, illustrating proof-of-concept for target-guided natural product development in RB[37]. However, there are practically no registered clinical trials investigating phytochemicals specifically in retinoblastoma, with clinical insights being extrapolated from adult oncology or other ocular diseases. These highlight a wide bench-to-bedside gap[87].

3.3 Key Translational Challenges

A major obstacle is the lack of standardised, reproducible phytochemical preparations. Indeed, different extraction methods, plant parts, harvest conditions and storage may markedly alter the qualitative and quantitative profile of the active constituents, resulting in batch-to-batch variability in potency and safety[88]. Modern standardisation requires botanical authentication, chromatographic fingerprinting (HPLC, HPTLC, GC), quantification of marker compounds, stability testing and GMP to ensure consistent dose-response relationships, which few anti-RB plant preparations currently fulfil.

The pharmacokinetics of phytochemicals in children with intraocular tumours remain poorly characterised. Most compounds are known to have low oral bioavailability, extensive hepatic and intestinal metabolism, and active efflux, while ocular distribution, vitreous and retinal concentrations, and elimination in pediatric eyes are seldom reported. Another critical concern related to children is safety: Developmental differences in drug metabolism and organ sensitivity require rigorous dose-finding and toxicity studies, yet most reports rely on *in vitro* assays or animal models that do not reflect long-term effects, immunotoxicity, or the potential impact on growth and neurodevelopment[89].

Herb-drug interactions pose additional risks when phytochemicals are combined with standard retinoblastoma chemotherapy (vincristine, etoposide, carboplatin) or emerging targeted drugs. Comprehensive reviews in oncology document that herbal products can modulate cytochrome P450 enzymes, transporters, and pharmacodynamic targets, leading to reduced efficacy, increased toxicity, or unpredictable responses of anticancer drugs[90]. Regulatory frameworks for herbal medicines and nutraceuticals are often less stringent than for conventional drugs and vary between jurisdictions; ensuring quality, efficacy, and safety for pediatric oncology use would require phytochemicals intended for RB to be developed under full pharmaceutical standards, with clear guidance on

Table 2. Nanocarrier-based delivery of phytochemicals, molecular targets and key findings in retinoblastoma

Phytochemical/ Extract	Plant source	Nanocarrier type and key features	Molecular targets/ pathways	Main findings
Curcumin and Epigallocatechin Gallate (EGCG)	*Curcuma longa*, green tea	Tumortargeted NPs for ocular tumours	PI3K/AKT, NF-κB	Higher retina/choroid levels after local injection, prolonged intraocular residence[75-77]
Curcumin	*Curcuma longa*	Polymeric NPs (PLGA, PEGylated: 100-200 nm)	AKT, NF-κB	↑ Solubility and stability, ↑ uptake, stronger AKT/NFκB inhibition and apoptosis vs. free drug in tumor models[78,79]
Resveratrol	Grapes	Polymeric or lipid NPs (PLGA, SLN)	PI3K/AKT, apoptosis pathways	Sustained release, enhanced antiproliferative and proapoptotic effects in cancer cells[80]
Lisosan G	Wheat extract	Liposomes/niosomes for retinal delivery	Antioxidant pathways	Higher retinal levels and better retinal protection vs. free extracts[81,82]
Flavonoids (*e.g.*, quercetin)	Onion, apple	Niosomes (Span/ Tween + cholesterol)	PI3K/AKT, VEGF	Improved corneal/scleral permeation and uptake, reduced acute toxicity in ocular models[83,84]
Berberine	*Berberis*	Chitosanbased NPs	PI3K/AKT, NF-κB	Better stability and cellular uptake, improved anticancer activity *in vitro*[85]

quality control, clinical evaluation, and post-marketing surveillance[91].

3.4 Future Directions and Perspectives

Therefore, future work should pursue target-guided screening strategies that match plant-derived compounds to distinct molecular vulnerabilities in retinoblastoma. PLK1 represents one such exciting example: xenograft and patient-derived data indicate that PLK1 is overexpressed and functionally important in RB, and natural products, including xanthatin, were identified via phenotypic screening and transcriptomic analysis as PLK1-modulating agents[92]. Similar in silico docking and structure-based screening platforms could prioritise phytochemicals against other RB-relevant targets, including CDK4/6, CDK2, PI3K, AKT, and anti-apoptotic Bcl-2 family proteins, as highlighted by various docking-based studies on plant-derived inhibitors of CDK4 and related kinases[93].

Other key directions for further research are combination strategies with existing RB regimens. Preclinical evidence in other cancers suggests that phytochemicals can enhance the efficacy of chemotherapy or radiotherapy by modulating PI3K/AKT/mTOR, NF-κB, and oxidative-stress pathways, thus offering an opportunity to reduce the dose of cytotoxic drugs while preserving their clinical efficacy[94]. In the context of retinoblastoma, rational combinations—such as phytochemicals targeting PLK1 combined with intra-arterial melphalan or compounds modulating CDK combined with vincristine, etoposide and carboplatin should be investigated in orthotopic animal models using clinically relevant dosing schedules and pharmacokinetic-pharmacodynamic correlations[95].

Personalised and chemopreventive approaches also deserve consideration. High-risk carriers of germline RB1 mutations and survivors at risk of second primary cancers could, in principle, gain from well-characterised phytochemicals with demonstrated chemopreventive activity, if safety and interaction profiles are well defined[96]. Integration of genomic, transcriptomic, and pathway analysis from individual tumours, including identification of PLK1 overexpression, MYCN amplification, and other actionable alterations, could inform selection of phytochemical combinations tailored to the molecular landscape of each patient[78].

Critically, progress depends on robust preclinical pipelines and well-designed clinical trials. This includes standardised *in vitro* testing across multiple RB cell lines, mechanistic validation, and advanced *in vivo* models-orthotopic xenografts, transgenic or patient-derived models-that incorporate realistic ocular pharmacokinetics and delivery routes[97]. Only after comprehensive toxicology, pharmacokinetics, and interaction studies should early-phase pediatric

trials be initiated, starting with carefully monitored adjunctive use alongside standard therapy, with clear endpoints for safety, tumour control, eye salvage, vision preservation, and long-term outcomes.

4. Conclusion

Phytochemicals and plant-derived agents are promising adjuncts or even future alternatives in the therapy of retinoblastoma because they may modulate a variety of pathways that are dysregulated in disease, including cell-cycle regulators, PI3K/AKT/mTOR, MAPK/ERK, JAK/STAT, NF-κB and angiogenesis-related signalling. Their induction of apoptosis, inhibition of proliferation, and suppression of invasion and neovascularisation against a variety of molecular targets show congruence with the complex biology of RB and suggest possible synergy with existing chemotherapy and locoregional approaches.

The translational landscape, however, remains largely preclinical, with *in vitro* studies and a few animal models dominating the landscape but lacking dedicated clinical trials in RB to date, underscoring a significant gap between mechanistic promise and clinical implementation. Key challenges, such as nonstandardised extracts, incomplete pharmacokinetic and safety data in children, uncertain interactions with standard chemotherapy, and heterogeneous regulatory pathways, must be addressed to integrate phytochemicals safely and reliably into RB management algorithms. Overcoming this bench-to-bedside divide will require strict standardisation, rational target-guided screening, such as PLK1 and CDK4-directed discovery, combination studies with existing RB regimens, and well-designed preclinical and clinical trials that define their true therapeutic value in retinoblastoma.

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Author Contribution

Qusai Malak was responsible for conducting the literature search and preparing draft of the manuscript. Rupa Mazumder contributed to the conceptualization of the study and provided critical revisions to refine the manuscript. Anjna Rani and Rakhi Mishra thoroughly reviewed the manuscript and granted the final approval for submission. All authors have read and agreed to the published version of the manuscript.