

Retinal Toxicity Induced by Chemical Agents

Subjects: Ophthalmology

Contributor: Daniel Souza Monteiro de Araújo, Rafael Brito, Dannel Pereira-Figueiredo, Alexandre dos Santos-Rodrigues, Francesco De Logu, Romina Nassini, Andrea Zin, Karin C. Calaza

Vision is an important sense for humans, and visual impairment/blindness has a huge impact in daily life. The retina is a nervous tissue that is essential for visual processing since it possesses light sensors (photoreceptors) and performs a pre-processing of visual information. Thus, retinal cell dysfunction or degeneration affects visual ability and several general aspects of the day-to-day of a person's lives. The retina has a blood–retinal barrier, which protects the tissue from a wide range of molecules or microorganisms. However, several agents, coming from systemic pathways, reach the retina and influence its function and survival. Pesticides are still used worldwide for agriculture, contaminating food with substances that could reach the retina. Natural products have also been used for therapeutic purposes and are another group of substances that can get to the retina. Finally, a wide number of medicines administered for different diseases can also affect the retina. Here gathers recent information about the hazard of these products to the retina, which could be used to encourage the search for more healthy, suitable, or less risky agents.

Keywords: pesticides ; medicinal herbs ; natural products ; medicinal ; retina

1. Introduction

The retina is responsible for light transduction and for preprocessing this information with an intraretinal circuitry. The mature vertebrate retina is located at the back of the eye, and it is organized in layers ^{[1][2]}. In the outermost portion of the retina, closer to retinal pigmented epithelium (RPE), lies the outer nuclear layer (ONL) formed by the cell bodies of cones and rods photoreceptors; the next nuclear layer, toward vitreal surface, is the inner nuclear layer (INL), composed of the cell bodies of horizontal, bipolar, amacrine, displaced ganglion cells, and in some species, interplexiform cells. Closest to the vitreal part of the retina, there is the ganglion cell layer (GCL) consisting of the cell bodies of ganglion cells, displaced amacrine cells, and a few photosensitive ganglion cells. Interspersing these nuclear layers are the outer plexiform (OPL) and inner plexiform (IPL) layers, where synaptic contacts occur. The axons of ganglion cells give rise to the optical fiber layer (OFL), becoming the optic nerve as these fibers leave the retina, sending the information to areas of the brain responsible for visual processing ^{[1][3]}.

In the retina, specialized cells develop relevant functions in visual processing, with cone cells working in daylight conditions (photopic), whereas rods function in dim light conditions (scotopic) ^[4]. Photoreceptors synapse with specific rod- or cone-bipolar cells and horizontal cells in the OPL. Each bipolar cell, in turn, synapses with ganglion cells. Therefore, the transduced light information travels through the excitatory vertical/radial pathway ^{[1][5]}, which is modulated by horizontal and amacrine cells, respectively in the OPL and IPL, by inhibitory synapses composing the horizontal/lateral pathway.

Besides neurons, the retina also presents three types of glial cells: Müller, astrocyte, and microglia. The Müller glia is the predominant glial cell type (90% of glial cells), with the cell body located in the middle of the INL and radial processes that extend through all layers of the retina. Müller glia perform several functions crucial to the homeostasis and physiology of the retina, including pro-survival signaling, synaptic regulation, neuronal activity modulation, extracellular potassium buffering, water elimination, regulation of blood–retinal barrier (BRB) and neurovascular coupling ^{[6][7][8][9]}. Astrocytes are restricted to the innermost part of this tissue, in the OFL and GCL. At these sites, astrocytes have a neurotrophic support role, interact with blood vessels participating in the BRB assembly and neurovascular coupling, and can react to pathological signs by adopting a gliosis pattern ^{[10][11]}. Microglia are mononuclear phagocytes that enter the retina during development ^{[12][13]}. Although microglia can be sparsely found in almost all retinal layers, the great majority resides in the OPL and IPL ^[13]. Microglia are also important players in the maintenance of the retinal homeostasis, responding to neural signs that switch the microglia state (in a simplistic way from ramified vigilant to ameboid reactive cell), probably contributing to retinal visual function ^{[14][15][16]}.

Most mammals have intraretinal blood vessels supporting the energy demands of the inner retina. Human retina has a peripapillary plexus in the innermost part of the NFL and inner (in the GCL) and outer (in the IPL, INL to OPL) intraretinal beds. Interestingly, the primate specialized region for high visual acuity, the fovea, is avascular, minimizing light distortion [17]. Similar to the brain, intraretinal vessels have a specialization, tight junctions between the endothelial cells, that guarantees retinal protection, and it is called BRB. Finally, the source of blood supply for the outer retina, the photoreceptors layer, is the choroidal vascularization, which is vast but has no BRB.

Between the retina and choroid stands the RPE, which plays several important roles to support retinal function. RPE is a monolayer of pigmented epithelial cells which absorb unprocessed light, contributing to a high visual acuity. RPE also contributes to the recycling of molecules of the visual cycle and to the transport of oxygen and nutrients coming from choroidal vessels to the photoreceptor. Finally, RPE forms an outer BRB through tight junctions present between RPE cells, and malfunctioning/degeneration of RPE is associated to diseases such as age-related macular degeneration (AMD) and Stargardt disease [16][18].

A wide variety of substances, such as quinolines, phenothiazines, and antiretroviral drugs reach the retina through the vascular supply. While beneficial therapeutically, several ocular and systemic drugs are responsible for causing retinal damage. Usually, toxicity is reversible following discontinuation of the provoking drug. Nevertheless, permanent or progressive vision loss may occur in a few cases.

Besides medicines, other substances can also reach the retina and can influence retinal function and health. Several chemical agents used as pesticides are hazardous to health, and specifically to the retina.

2. Natural Products

In an evaluation of retinas from the National Toxicology Program bioassay database, Yamashita and co-workers (2016) [19] demonstrated that retinas from a 2-year carcinogenicity study with kava kava extract (KKE) showed a significant increase in degeneration. KKE is derived from the root of the tropical shrub *Piper methysticum*, and it was originally used for ceremonial beverages in the South Pacific. Both males and females exhibited features of retinal degeneration after 0.3 g/kg or 1.0 g/kg KKE dose [19]. In a subsequent study, the group demonstrated that F344N rats dosed with KKE 1.0 g/kg for 90 days did not show signs of retinal degeneration. However, the RPE, only from the superior retina, had a reduced number of phagosomes [20]. The authors speculated that this result could indicate an impairment in photoreceptor outer segment phagocytosis by RPE cells, which could affect the health of the retina after the 2-year exposure observed in the previous study.

Another compound that has been studied due to its potential anticancer properties [21] is hypericin, a polycyclic aromatic naphthodianthrone that occurs naturally. It has been previously shown that hypericin induced cell death of human and bovine isolated RPE cells [22][23]. A more recent study showed that an acute exposure of isolated bovine retinas to hypericin caused a reduction in the amplitude of the b-wave in an electroretinogram recording, indicating an impairment in retinal function.

Embelia ribes possess significant potential in the prevention and treatment of several chronic diseases, including arthritis, bacterial infections, cancer, cardiovascular diseases, diabetes, neurological problems, and wound healing [24]. *Hagenia abyssinica* (Rosaceae) is one of the most-used medicinal plants for the treatment of diarrhea and to treat diabetes mellitus in some regions of Africa [25][26]. Post-hatched chicks orally received treatment either with a high dose of 0.25 g (5 g/kg per day) or a low dose of 0.025 g (0.5 g/kg per day) of *Embelia ribes* for 1 or 5 days or *Hagenia abyssinica* for 1 or 9 days. Both compounds impaired visual function (visual discrimination and stimulus detection in the peripheral visual field). High doses of both agents induced degeneration of the ganglion cell layer [27].

Several studies have shown a protective effect of curcumin in different pathological models, such as diabetic retinopathy and ischemia and light-, oxidative stress-, and N-Methyl-D-Aspartate (NMDA)-induced cell death, among others [28][29][30][31][32][33]. However, in one study, curcumin induced apoptosis in mouse-rat hybrid retina ganglion cells, called N18 [34]. Similarly, but with fewer studies, garlic or some of its bioactive compounds show a protective effect in several pathological models. Yet, 24-h exposure to diallyl disulfide (DADS) induced a dose-dependent reduction in N18 cell viability [35]. DADS induced increase in ROS, intracellular calcium and activation of the classic apoptosis mediator, caspase-3 [35].

Concerning natural products, it is important to note the huge number of studies showing protective effects of these substances in animal models of distinct retinal diseases. However, several of these natural herbs/medicines were not tested or fail to show protective effects or, even worse, can be toxic to retinal humans [36][37]. Therefore, clinical studies seem to be extremely important to confirm/reject data from animal models.

3. Drugs and Medicine

Despite the BRB, the retina is susceptible to harmful effects of systemic, intravitreal, or topical drugs leading to dysfunction and retinal degeneration. Retinal drug toxicities can be expressed in many ways: disruption of RPE and photoreceptor complex, vascular damage, ganglion cell or optic nerve, cystoid macular edema, crystalline retinopathy, or ganglion cell or optic nerve injury (**Figure 1**).

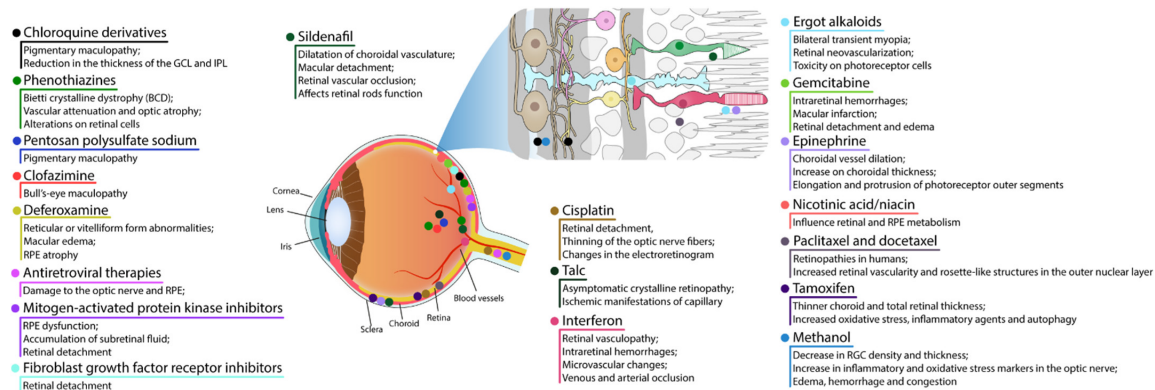


Figure 1. Schematic figure showing the areas affected by some drugs. Alterations in retinal vessels and RPE are represented in the eye whereas impact in retinal cell are showed in the retinal scheme.

3.1. RPE and Photoreceptor Complex

The most common presentation of alteration in RPE and photoreceptor complex is pigmentary maculopathy (**Figure 2**).



Figure 2. Fundus image: white arrow shows a concentric epithelial degeneration around the fovea, called bull's eye maculopathy.

3.1.1. Chloroquine Derivatives

Chloroquine (CQ) and its derivative, hydroxychloroquine sulfate (HCQ), are immunomodulatory drugs that are prescribed for malarial prophylaxis and to treat autoimmune conditions such as rheumatoid arthritis or systemic lupus erythematosus. Both medications bind to melanin in the RPE and uveal tissue and can affect metabolic function. Prolonged use of the CQ derivatives typically results in a pigmentary maculopathy (**Figure 3**). The incidence of retinopathy in patients treated with CQ is approximately 10 to 20% [38].

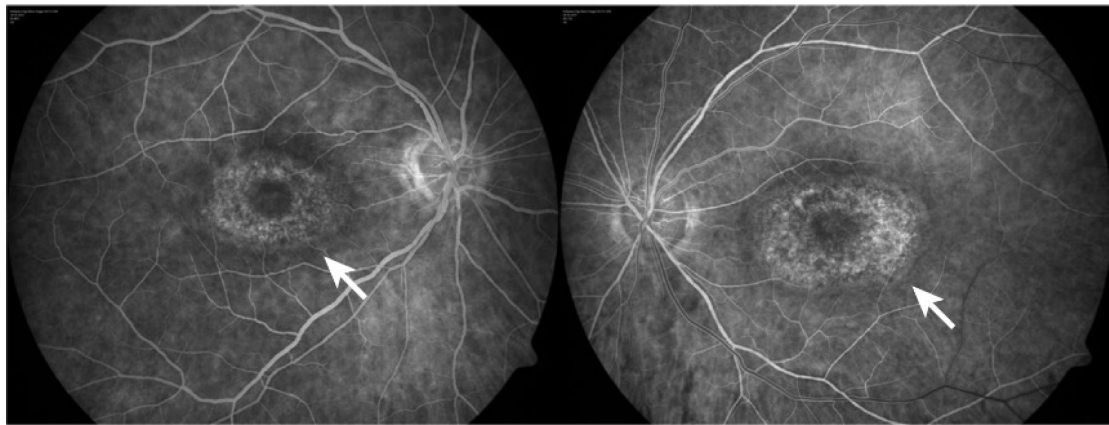


Figure 3. Hydroxychloroquine toxicity: white arrow shows presence of parafoveal zone of hyperfluorescence on fluorescein angiography.

The classic presentation is a bull's eye-maculopathy appearance where the fovea is surrounded by a ring of depigmentation followed by a ring of hyperpigmentation (**Figure 2**). In the advanced stages of toxicity, the pigment abnormalities can involve the peripheral retina with a clinical picture that resembles primary tapetoretinal degeneration with optic disc pallor, retinal vessel attenuation, and bone spicules. Visual acuity is affected when the pigmentary abnormalities involve the center of the fovea. The risk of toxicity is dependent on daily dose and duration of use. At recommended daily doses (maximum of 5.0 mg/kg real body weight for HCQ; 2.3 mg/kg real body weight for HQ), the risk of toxicity up to 5 years is under 1% and up to 10 years is under 2%, but it rises to almost 20% after 20 years. However, even after 20 years, a patient without toxicity has only a 4% risk of converting in the subsequent year. Treatment should be stopped at the first sign of toxicity; otherwise, toxic effects continue to progress despite discontinuation of the drug [38] [39].

Unlike RPE-1 cells, which apparently do not suffer cell damage upon exposure to CQ, the ARPE 19 cells die after treatment with this drug [40][41]. Increasing concentrations with CQ (10–100 μ M) led to the death of these cells in culture after 24 h of administration, with the same being found in primary cultures of pigmented epithelium of mice. The observed cell death depended on the induction of apoptosis, as seen by the reduction of the anti-apoptotic proteins B-cell lymphoma 2 (Bcl-2) and B-cell lymphoma-extra-large (Bcl-xL) and the increase of the pro-apoptotic proteins BAX and BID [41]. Furthermore, the death of ARPE 19 cells is involved with the inhibition of autophagy. The authors demonstrated a large intracellular vacuolization, which was accompanied by an increase in LC3-A/B, Beclin-1, and p62. The accumulation of autophagy-related proteins was likely due to a weakening of autophagosome–lysosome fusion [41]. The induction of apoptosis and inhibition of autophagy by chloroquine were related to increased phosphorylation of p38 and JNK protein kinases, both responsible for mammalian target of rapamycin (mTOR) phosphorylation. In turn, mTOR induced an increase in the interaction between Beclin-1 and Bcl-2. The interaction between these two proteins causes a mutual inhibition, which explains the effect of chloroquine on apoptosis and autophagy [41]. Interestingly, concomitant exposure with D4476, a casein kinase inhibitor, reversed CQ-evoked effects, demonstrating a key role of casein kinase in controlling apoptosis and autophagy via p38, JNK, and mTOR [41]. Altogether, these works show the neurotoxic mechanisms associated with CQ-induced retinopathy, although little is known about its effects on retinal neurons.

3.1.2. Phenothiazines

Thioridazine and chlorpromazine are used as antipsychotics to treat schizophrenia and other psychiatric disorders. The exact mechanism of retina lesion is not known, nevertheless it may involve enzyme disruption and abnormal rhodopsin synthesis.

Chlorpromazine toxicity is rare, being more commonly observed with thioridazine due to its piperidyl side chain. Both chlorpromazine and thioridazine accumulate in the melanin of RPE and uveal tissue. In the early stage, there is RPE stippling in the posterior pole; at a later stage, nummular areas of RPE/choriocapillaris loss are seen from the posterior pole to mid-periphery. The late-stage mimics choroideremia or Bietti crystalline dystrophy (BCD), and vascular attenuation and optic atrophy are seen [42][43]. The early fundus abnormalities often advance despite discontinuation of the medication.

The risk of retinopathy is more dependent on total daily dose rather than cumulative amount received. Thioridazine toxicity at dosages less than 800 mg/day is rare, though cases have been reported with lower doses over several years. Regardless of the dose, patients taking thioridazine should be regularly monitored for signs of toxicity [42][43]. A recent

study using human retinal organoids, on day 150 of differentiation, showed that thioridazine (135 μ M, 24 h) induced a wide range of alterations [44]. Thioridazine induced the expression of genes related to oxidative stress, inflammation, and cell death. Unsurprisingly, an increase in the percentage of cells labeling to chemokine (C-C motif) ligand 2 (CCL2), triggered and released in inflammatory conditions, and to α -crystallin (CRYAB), involved in the protection of cells from stress by binding misfolded proteins, was observed. Classical signals of glia activation were also demonstrated. Accordingly, a widespread reduction of retinal cells (photoreceptors, horizontal, amacrine, Müller glia, and retinal ganglion cells) accompanied by a decrease of approximately 50% in neuroepithelium thickness was shown [44].

3.1.3. Pentosan Polysulfate Sodium

Pentosan polysulfate sodium (PPS) is used for the treatment of interstitial cystitis and is associated with a pigmentary maculopathy. Usually, toxicity is more common in women, after chronic use for over 15 years, and in patients exposed to more than 1500 g [45]. Common symptoms include blurred vision, difficulty reading, metamorphopsia, paracentral scotomas, and prolonged dark adaptation. Signs comprise parafoveal pigmented deposits at the level of the RPE, vitelliform deposits, and patchy paracentral RPE atrophy similar in appearance to pattern dystrophy [45][46][47]. Since PPS is an inhibitor of heparanase, used chronically, a study investigated the consequence of the absence of this enzyme in knockout mice (KO) [48]. Heparanase KO mice at 3-, 9- and 15-weeks-old showed lesions in the retina (central and peripheral), RPE folds, choroidal thickening, cells detached from RPE, increased ONL thickness, and retinal disorganization. The damage in RPE/choroid seemed to progress over time from moderate RPE/choroid changes in 3- and 9-week-old KO mice to severe choroid/RPE protrusions in 58% and 75% for 9- and 15-week-old KO, respectively. There were no signals of proliferation and recruitment of macrophages cells, thus concluding that the RPE protrusions are not related to inflammatory signals from recruited cells.

3.1.4. Clofazimine

Clofazimine is a phenazine dye with anti-mycobacterial and anti-inflammatory action. It binds preferentially to mycobacterial DNA by inhibiting DNA replication and cell growth and is used to treat dapsone-resistant leprosy and autoimmune disorders such as psoriasis and lupus. Ocular side effects include bull's-eye maculopathy. Drug discontinuation can halt progression but retinopathy does not regress [49].

3.1.5. Deferoxamine

Deferoxamine (DFO) is used as a chelating agent to treat iron toxicity/overload. Signs of toxicity are reticular or vitelliform form abnormalities and/or macular edema due to RPE pump failure. Retinopathy includes several pattern dystrophy-like changes or minimal changes affecting the RPE–Bruch membrane–photoreceptor complex. Multimodal imaging confirms histology findings that photoreceptor outer-derived retinoids, fluorophores, and RPE displacement or clumping are entangled in DFO retinopathy, leading to unequivocal RPE atrophy in many cases of pattern dystrophy-like changes. Drug cessation can reverse established mild retinopathy. Nevertheless, when exposure is prolonged, RPE and outer retina damage may persist [50]. Nonetheless, iron chelant, including deferoxamine, has been shown to protect retinal cells in different degenerative models, such as NMDA-induced excitotoxicity [51], cell death promoted by oxidative stress in ARPE 19 cells [52][53], or 611 photoreceptor lineage cells [54] by blocking ferroptosis.

3.1.6. Antiretroviral Therapies

Even though antiretroviral drugs can help arrest human immunodeficiency virus (HIV) progress or other infection-associated retinal disease, an undesirable rare retinal toxicity could occur [55]. Didanosine (DDI) is a nucleotide reverse transcriptase inhibitor used to treat individuals with acquired immunodeficiency syndrome (AIDS), probably because it inhibits polymerase ($\text{pol-}\gamma$), the enzyme responsible for replication and repair of mitochondrial DNA. DDI can cause mitochondrial dysfunction and toxicity resulting in damage to the optic nerve and RPE; peripheral field loss occurs with concentric loss/mottling of RPE (areas of chorioretinal atrophy), beyond arcades to mid-periphery, bilaterally symmetrical [56] (Figure 4).

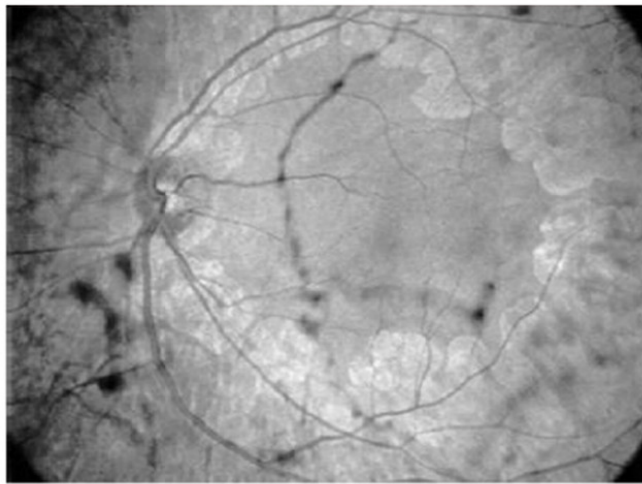
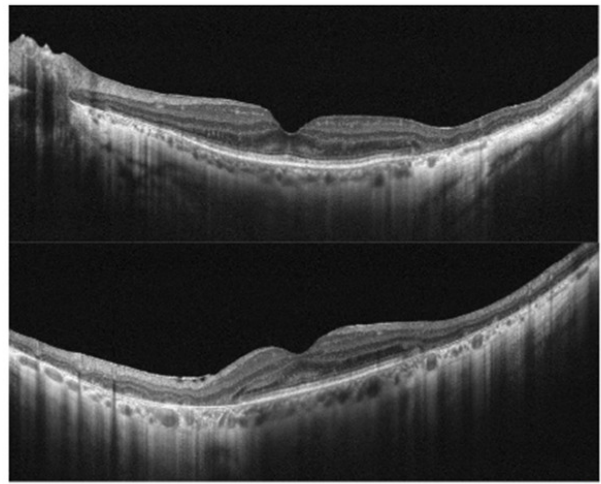
a**b**

Figure 4. Multimodal imaging: **(a)** infrared light retinography shows confluent plaques of chorioretinal atrophy in posterior pole, with the macular area more preserved; **(b)** OCT shows marked impairment of the outer neurosensory retinal layer, retinal pigmented epithelium, and perifoveal choroid. Diffuse thinning is seen with marked atrophy of the outer nuclear layer, external limiting membrane, and ellipsoid zone. Diffusely increased posterior light reflectance demonstrates associated retinal pigmented epithelium atrophy. The foveal area maintains normal architecture but shows slightly increased internal reflectivity of the outer nuclear layer.

3.1.7. Mitogen-Activated Protein Kinase Inhibitors

Mitogen-activated protein kinase (MEK) inhibitors (trametinib (Mekinist), cobimetinib (Cotellic), binimetinib (Mektovi), and selumetinib (Koselugo)) are used to treat metastatic melanoma. The toxicity mechanism is thought to be due to RPE-induced dysfunction with subsequent accumulation of subretinal fluid. The most common structural abnormality found is bilateral multifocal serous retinal detachment with at least one focus involving the fovea. Onset can occur shortly after initiation of therapy. Visual symptoms are typically minimal with the fluid often spontaneously resolving. For persistent cases, discontinuation of the drug usually leads to complete resolution [57].

Human neuroretina shows phosphorylated ERK, which is inhibited by binimetinib treatment [58]. Phosphorylated ERK status is recovered after ceasing MEK inhibitor treatment both in ARPE 19 cells and primary neuroretina cells from human tumor eyes [58]. These results indicate that the disappearance of retinopathy with the discontinuation of binimetinib treatment is associated with the reactivation of ERK.

3.1.8. Fibroblast Growth Factor Receptor Inhibitors

Fibroblast growth factor receptor (FGFR) inhibitors are chemotherapeutic agents used to treat cholangiocarcinoma and urothelial carcinoma [59]. Currently, FDA-approved drugs include erdafitinib, pemigatinib, and infigratinib [60]. FGFR inhibitors appear to cause serous retinal detachments, similar to MEK retinopathy. Few reports are available in the literature of FGFR retinopathy [61].

3.1.9. Sildenafil

Sildenafil is used to treat erectile dysfunction and pulmonary artery hypertension. It blocks phosphodiesterase 5, an enzyme that promotes breakdown of cyclic guanosine monophosphate (cGMP). A possible side-effect is dilatation of choroidal vasculature and secondary serous macular detachment, and retinal vascular occlusion can occur [62].

Mice treated with sildenafil showed a reversible increase in maximal retina vessel dilatation and choroid effusion promptly after intravitreal injection and 30 min after intraperitoneal injection [63]. In 5% of mice, sildenafil provoked RGC loss and damage of optic nerve after 21 days of the treatment. In an in vivo approach to evaluate the effect of sildenafil in the mouse retina, QUench-assISTed (QUEST) magnetic resonance imaging (MRI) was used in subretinal space using QUEST optical coherence tomography (OCT), while QUEST optokinetic tracking (OKT) was used for cone-based vision [64]. QuestMRI showed an increase in oxidative stress in a group treated with sildenafil when compared to a group exposed to sildenafil plus antioxidants. This effect was only detected in the peripheral superior retina [64]. Levels of ROS evaluated by DCF staining in freshly isolated retinal sections were higher all over the retina treated with sildenafil compared to saline, with more prominent labeling in the superior retina. ONL thickness was constant regardless of treatment with sildenafil or antioxidants. At 5 h post-sildenafil treatment, contrast sensitivity was significantly lower-than-normal and similar even in the presence of antioxidants.

3.1.10. Cisplatin

Cisplatin (cisdiamminedichloroplatinum—CIS) has been used effectively for years as a chemotherapy drug in the treatment of solid tumors, metastases, and small cell cancers with unknown primary tumors [65]. Despite its success in inducing tumor death and remission of associated symptoms, several studies report side effects related to the visual system in patients treated with CIS. In these cases, partial loss of vision, retinal detachment, thinning of the optic nerve fibers, changes in the electroretinogram, occlusion of the middle retinal, and cilioretinal arteries have already been demonstrated [66][67][68][69]. At the cellular level, the cytotoxicity of CIS was confirmed in ocular tissue cells of different species. In rat retinas, a single intraperitoneal injection with CIS (16 mg/kg) increased the levels of MDA, as well as decreased the levels of reduced glutathione (GSH). Immunohistochemical assays revealed an increase in labeling for 8-hydroxy-2p-deoxyguanosine (marker of DNA damage) in horizontal cells and for endothelial nitric oxide synthase (eNO) in retinal blood vessel cells [70]. Blood samples from rats administered for 14 days with CIS (2.5 mg/kg) also revealed an increase in MDA, myeloperoxidase (MPO), and the levels of the total oxidant system, but also in the pro-inflammatory cytokines, including the tumor necrosis factor alpha (TNF- α) and interleukin-1 β (IL-1 β). At the same time, there was a reduction in GSH, SOD activity, and levels of the total antioxidant system [71][72][73]. After treatment with CIS, the retinal tissue showed degeneration, edema, and vascular congestion with disorganization of the retinal layers. Optic nerve tissue anomalies have also been observed, such as destruction, hemorrhage, edema, and an increase in the number of astrocytes and polymorphonuclear leukocytes [70][71][72][73].

3.2. Retinal Vascular Damage

Many drugs can damage the retinal vasculature, by inducing a hypercoagulable state, or by particle clogging of blood vessels. Some might be used as intraoperative ocular medications as aminoglycosides, moxifloxacin, or vancomycin.

3.2.1. Talc

Talc retinopathy is characterized by the presence of small, yellow crystals located in small retinal vessels and within different retinal layers. Ocular damage usually develops after chronic intravenous drug abuse and manifestations range from asymptomatic crystalline retinopathy to severe ischemic manifestations of capillary non perfusion. The presence of crystals is thought to be secondary to emboli derived from talc, which is an insoluble inert particulate filler material used in some oral (methylphenidate hydrochloride, methadone, pentazocine, and amphetamine), inhaled (crack cocaine), and intravenous (cocaine and heroin) preparations.

3.2.2. Interferon

Interferons are classified into three major types—INF- α , INF- β , and IFN- γ —and have been used for treatment of different pathologies, including Kaposi sarcoma, hepatitis B and C, multiple sclerosis (MS), and malignant osteopetrosis. Systemic therapy has been associated with retinal vasculopathy characterized by cotton wool spots, intraretinal hemorrhages, microvascular changes including capillary drop-out, CME (typically in the posterior pole and peripapillary region), venous occlusion, or arterial occlusion, consistent with ischemic retinopathy [74]. The exact mechanism of toxicity is not known but may involve impairment of retinal microcirculation. Changes typically present 4–8 weeks after initiation of therapy and usually regress after treatment cessation [74].

Shed light on these molecules as central regulators and not just inflammatory markers. Among these three types of interferon, only IFN- γ was related to possible retinal injurious effects. Roche and collaborators (2018) reported that IFN- γ released by microglia induces pSTAT3 signaling in Müller cells and increases glial fibrillary acidic protein (GFAP) expression [75]. These results were explored in the context of the retinitis pigmentosa (rd10) mouse model, which increased GFAP staining throughout time. IFN- γ was also linked to the increase of BRAF-activated non-coding RNA (BANCR), a long non-coding RNA involved in the inflammatory context of RPE dysfunction associate to diseases like AMD, acting through signal transducer and activator of transcription 1 (STAT1) phosphorylation in ARPE-19 cells [76]. This increase was progressive, reaching up to 30 times higher concentration of the RNA when treated with 100 units/mL of IFN- γ . In addition, in ARPE-19 cells and in this context of inflammation and AMD progression, IFN- γ (50 ng/mL–48 h) induced cell death [77].

Controversially, in a context of diabetic retinopathy, diabetic mice lacking IFN- γ showed a more than two-time increase in the mRNA expression of vascular endothelial growth factor (VEGF), intercellular adhesion molecule 1 (ICAM-1), retinoic-acid-receptor-related orphan nuclear receptor gamma (ROR- γ t), a transcription factor of immune cells T helper (Th) 17 cells, and a more than ten-times increase in splenic IL-17-producing CD4⁺ cells in comparison to diabetic mice [78]. Meanwhile, IFN- γ shows an anti-angiogenic effect in a mouse model of oxygen induced retinopathy (OIR) [79]. These data

show a role for IFN- γ as a critical regulator of inflammation and a possibility to explore it as a tool given its role as an inflammatory cytokine regulated in eye disease.

3.2.3. Ergot Alkaloids

Ergot alkaloids are mycotoxins produced by many fungal species of the *Claviceps* genus. There are four main types of ergot alkaloids: clavines, lysergic acids, lysergic acid amides, and ergopeptides. One of these ergopeptides is dihydroergotamine, which has been extensively used in the treatment of migraine. The antimigraine effect is mainly related to its agonist activity at 5-hydroxytryptamine receptor 1B (5-HT_{1B}), 5-hydroxytryptamine receptor 1D (5-HT_{1D}), and 5-hydroxytryptamine receptor 1F (5-HT_{1F}) receptors [80]. One case report described that one patient that received for the first time the oral medication Cefalium, a medication used to treat migraine, which contains dihydroergotamine in the formula, presented some ocular anomalies such as acute bilateral transient myopia, retinal folds, and island of choroidal delay after one day of treatment. The interruption of the treatment was able to solve all clinical symptoms [81].

Dopaminergic agonists derived from ergot are a group of drugs consisting of bromocriptine, cabergoline, dihydroergocryptine, lisuride, and pergolide. They have been available on the market for many years and are mainly used to treat Parkinson's disease, either alone or in combination with other medicines. A recent report described that knockout mice of rod transducin G protein subunit alpha transducin 1 (Gnat1), visual arrestin 1 (ARR1), or rhodopsin kinase 1 (GRK1) showed light damage and robust retinal inflammation after bright light exposure [82]. The pretreatment with metoprolol plus tamsulosin and bromocriptine protected the retina in all genetic knockout mice [82]. Abnormalities of angiogenesis are very common in age-related macular degeneration and proliferative diabetic retinopathy. In a study with a zebrafish animal model, retinal neovascularization induced by cobalt chloride promoted hypoxia. Pre-incubation with bromocriptine, cabergoline, pergolide, and all ergot-derived D2 dopamine receptor agonists significantly inhibited abnormalities of angiogenesis, decreasing mRNA expression levels of vascular endothelial growth factor Aa (VEGFAA) [83].

Lysergic acid diethylamide (LSD) is a potent synthetic psychedelic drug that can be derived from the ergot alkaloids. Visual changes are some of the effects after LSD use. One study investigated the effect of LSD on macrophage activation state and its toxicity to photoreceptor cells in vitro. They showed that the treatment of macrophage cultures with LSD induced a change to a pro-inflammatory profile [84]. LSD treatment of co-cultured macrophages with photoreceptors induced an increase in the oxidative stress markers and toxicity on photoreceptor cells [84]. Another study demonstrated that C57BL/6 mice treated with LSD had a decrease in electroretinography response and the loss of photoreceptor cells. This cell death of photoreceptors was mediated by upregulation of p-JAK1/p-STAT1 pathway [85].

3.2.4. Gemcitabine

Gemcitabine, a pyrimidine nucleoside analog, is a chemotherapy drug used as a treatment for different types of cancer, including bladder and breast cancer. Some studies have reported retinopathy associated with the use of this chemotherapeutic agent. One study demonstrated that one patient had several issues related to use of gemcitabine, such as a decrease in vision with appearance of cotton wool spots and intraretinal hemorrhages [86]. Another case report described that one patient had macular infarction after chemotherapy with gemcitabine and carboplatin [87]. More recently gemcitabine-associated retinal pathologies, such as presence of bilateral peripheral exudative retinal detachment, retinal edema, and Elschnig's spots, were also described [88].

3.3. Cystoid Macular Edema

Cystoid macular edema (CME) may occur after the treatment with fingolimod Gilenya for MS, topical prostaglandin analogs (e.g., latanoprost) for ocular hypertension or glaucoma, nicotinic acid (niacin) for lipid disorders, and/or paclitaxel treatment or DFO for iron toxicity/overload. Drug cessation results in resolution of the CME, although topical and local steroids or topical non-steroidal anti-inflammatory drugs have been used to facilitate resolution.

3.3.1. Epinephrine

Epinephrine, an endogenous molecule that can be used to treat cardiac arrest and anaphylaxis in a hospital environment, may also influence retinal physiology. Systemic adrenergic stimulation with isoproterenol, a β_1 - and β_2 -adrenergic receptors agonist, impact RPE renin expression, with implications on retinal pathophysiology [89]. The influence of stimulating the adrenergic system in the retina is not only related to changes in the renin-angiotensin system, but the stimulation can also affect RPE ion transport. Treatment with epinephrine induced a small, but rapid increase in what the authors called "short-circuit current" (current required to reduce the potential across the epithelial membrane to zero) [90]. Angiographic changes such as choroidal vessel dilation, increase on choroidal thickness, disruption and effacement of the

ellipsoid zone, and elongation and protrusion of photoreceptor outer segments have been reported after epinephrine treatment for 8 weeks in cynomolgus monkey [91].

3.3.2. Nicotinic Acid/Niacin

Nicotinic acid, also known as vitamin B, and its derivatives such as nicotinamide, can influence retinal and RPE metabolism. For instance, there is an established method for culturing ARPE-19 cells that uses nicotinamide to stimulate cell growth and differentiation [92].

3.3.3. Paclitaxel and Docetaxel

Paclitaxel and docetaxel are antineoplastic agents of the taxane class of drugs used in the therapy of many solid tumors, including breast and lung cancer. They act by promoting and stabilizing microtubule assembly, while preventing physiological microtubule depolymerization/disassembly in the absence of GTP. This leads to a significant inhibition of cellular mitosis and cell death [93]. There are several case studies reported in the literature linking retinopathies, such as phototoxic maculopathy and cystoid macular edema, induced by paclitaxel and docetaxel [94][95][96][97], but there are few reports about studies with these compounds in animal models or in vitro models. In C57BL/6J littermate pups, it was seen that paclitaxel treatment was able to reduce the number of retinal vascular branches in a dose-dependent manner during mouse retinal development in vivo [98]. Another study in a rat model showed that a single intraperitoneal injection of paclitaxel led to an increased retinal vascularity and rosette-like structures in the outer nuclear layer, a lesser number of astrocytes and oligodendrocytes, and some signs of cellular necrosis [99].

3.4. Crystalline Retinopathy

Tamoxifen

Tamoxifen is a selective estrogen receptor modulator and has been used to treat breast cancer. Retinopathy induced by tamoxifen is characterized by crystalline deposits and pseudocystic foveal cavitations. These findings are like macular telangiectasia type 2, suggesting a similar pathogenesis involving Müller cell dysfunction. Tamoxifen is associated with thinner choroid and total retinal thickness, suggesting that there were structural changes in patients without symptoms that could be early signs of RPE and photoreceptor damage. Toxicity is dependent on dose and length of use and typically manifests after 2-3 years. Visual function and macular edema typically improve after drug cessation, though the crystalline deposits remain [100][101] (Figure 5).

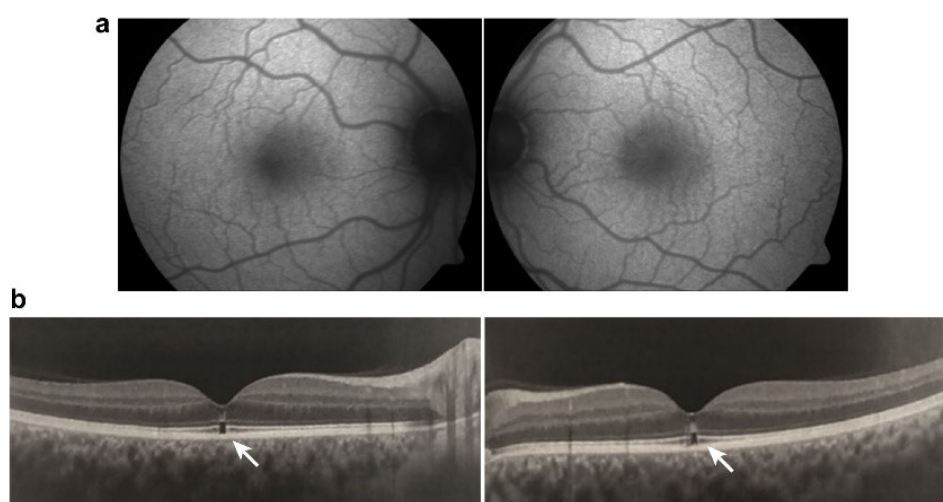


Figure 5. Tamoxifen retinopathy: (a) fundus autofluorescence image showing no abnormality; (b) optical coherence tomography: white arrow demonstrates ellipsoid foveal zone disruption and external limiting membrane hyperreflectivity.

Despite the recent in vitro data on RPE cells, in which tamoxifen is harmful, previous results have shown a protective role for the estrogen receptor modulator. Wang and collaborators (2017) observed that chronic tamoxifen (500 mg/kg—on diet) treatment prevented the effects of a mouse model of retinal light injury (LI) after 7 days, restraining the LI-induced retinal thickness decrease to almost zero, diminishing retinal detachment to less than 10% chance when compared to control, and normalizing ERG parameters. It also exerted a specific effect on rescuing the thickness of the outer retina, where the photoreceptors are located, correlating the results with diseases that promote photoreceptor degeneration, such as AMD, diabetic maculopathy, and retinitis pigmentosa. The protective effect was associated with more than 50% reduction in microglial activation and cytokine release promoted by the tamoxifen diet after 7 or 14 days of LI [102].

3.5. Damage to Ganglion Cell Layer or Optic Nerve

Methanol

Methanol intoxication is a very debilitating condition, most commonly found in developing countries where ingestion of contaminated alcohol in beverages could lead to a variety of systemic symptoms that range from mild intoxication, such as abdominal pain, nausea, vomiting, headache, general weakness, dyspnea and nervous system disturbances, including the retina, to more severe intoxication leading to renal failure, cardiovascular alterations, rhabdomyolysis, convulsions, coma and eventually death ^[103]. Visual symptoms might appear hours after ingestion, and they vary widely from progressive decrease in vision to dyschromatopsia, scotoma, and photophobia, accompanied by hyperemic and edematous optic disk acutely, while atrophy and pallor can be observed chronically ^[104]. The molecule itself is not the most alarming toxic agent, but rather, its metabolite, formic acid, represents a serious threat, being able to bind and inhibit cytochrome c oxidase, an enzyme of the mitochondrial respiratory chain, and therefore, inhibiting oxidative phosphorylation, causing ATP deficiency, and increasing oxidative stress, damaging a series of cellular components ^[103].

A decrease in RGC density and thickness alongside increased caspase-3 was also observed in a rat orally administrated methanol-induced toxicity model, an effect reversed by citicoline (1 g/kg/day) ^[105]. Very recently, Dorgau and colleagues (2022) aimed to establish a retinal organoid model to study drug toxicity and contribute to the development of treatment strategies ^[44]. The retinal organoids assemble from human pluripotent stem cells (hPSCs) and are arranged in a layered structure, expressing biomarkers for key cell types. Methanol treatment (32 mM–24 h) reduced the staining for middle/long wavelength cone opsin to almost zero, and although it did not change expressing markers for ganglion cells, it did reduce the number of active RGCs by half in response to white light pulses.

Moreover, in a rat methanol-induced toxicity study (3 g/kg—oral, for 7 days), Rutin (3,3',4',5,7-pentahydroxyflavone-3-rhamnoglucoside) or taxifolin (3,3',4',5,7-pentahydroxyflavanone), flavonoids found in vegetables and fruits, given after methanol ingestion, could prevent methanol induced increase in inflammatory markers (IL-1 β , NF- κ B and TNF- α) and oxidative stress markers (8-OHdG, MDA, MPO) in the optic nerve, alongside restoration of histologic pattern and avoidance of edema, hemorrhage, and congestion, suggesting an attenuation of optic neuropathy ^{[106][107]}.

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