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Effects and Pharmacological Use of Alkaloids on the Eyes

Jin-Ho Joo

Abstract

Alkaloids can have a variety of effects on the eyes. Some alkaloids are used as a treatment for eye diseases, such as keratoconjunctivitis, but they are also toxic to the retina. Other alkaloids are known to protect neuroretina from damage caused by oxidative stress. Numerous ophthalmic drugs, such as glaucoma and antibiotic eye drops, have long been developed through alkaloids. In this chapter, we will introduce the beneficial and detrimental effects of alkaloids on the eye. In addition, the action of alkaloids as existing eye drops and the possibility of developing them as drugs in the future will be discussed.

Keywords: alkaloid, eye, mydriasis, miosis, repurposing, myopia, presbyopia, intraocular pressure, retina, cataract, glaucoma, optic neuropathy, angiogenesis

1. Introduction

Alkaloid is a generic term for compounds derived from natural substances and having a nitrogen atom as a base. Alkaloids can be obtained from a variety of organisms, including bacteria, fungi, plants, and animals. The first alkaloid to be isolated was morphine from opium in 1804 by Friedrich Sertürner, a German pharmacist [1, 2]. Alkaloids with pharmacological effects are often known to be used as medicines, for example, physostigmine and pilocarpine as a treatment for glaucoma, and cocaine as a topical ocular anesthetic. However, in some cases, they are toxic, just as cocaine is highly toxic to corneal epithelial cells. Sometimes alkaloids cause undesirable constriction or dilation of the pupil, making us uncomfortable.

Recently, several studies have shown the potential of alkaloids as new drugs in the field of ophthalmology. Previously used, atropine plays a role in inhibiting the progression of myopia, and pilocarpine is attracting attention as a new treatment for presbyopia. In addition, some alkaloids are known to have antioxidant effects to prevent the progression of cataracts, protect the optic nerve through various mechanisms, and protect the retina by inhibiting angiogenesis.

Therefore, in this chapter, we would like to introduce the positive effects of using alkaloids as medicines and the various effects of alkaloids on the eyes. And among the recent studies, alkaloids would like to introduce the possibility of novel treatment in the field of ophthalmology.

2. Medicinal use of alkaloids in the field of ophthalmology

2.1 Atropine

Atropine ($C_{17}H_{23}NO_3$) is a drug widely used by ophthalmologists for ophthalmic diagnosis and treatment since the 1800s and not only derived from the leaves of *Atropa belladonna* but is also found in other plants mainly from the Solanaceae family, such as *Datura stramonium, A. belladonna, Hyoscyamus niger*, and *Mandragora officinarum* [3]. It is an anticholinergic drug that causes powerful and long-lasting mydriasis and paralyzes the ciliary body, causing cycloplegia. For muscarinic receptors, it competes with acetylcholine or muscarine to inhibit parasympathetic nerves and selectively block the action of acetylcholine or muscarine. Acetylcholine secreted by stimulation binds to muscarinic receptors to continue signal transmission, and then, acetylcholine must be degraded by an enzyme called "acetylcholinesterase" to continue normal signal transmission. Atropine binds to muscarinic receptors but does not cause signal transduction, and since atropine and acetylcholine competitively bind to muscarinic receptors, atropine acts to inhibit the action of acetylcholine [4].

Until now, atropine eye drops have been used in ophthalmology to make mydriasis for diagnosis and surgical treatment, to help reduce intraocular inflammation and control the spasm of the near reflex. Recently, low concentrations of atropine have been found to be effective in controlling myopia. In a randomized clinical trials study, it was known that 0.05% atropine was less effective at the optimal concentration and minimized the side effects of near blurry and photophobia [5, 6].

Although the mechanism by which atropine suppresses the progression of myopia is not known, the following hypotheses are known to be highly likely through several studies. First, atropine affects the sclera, which is a fibrous connective tissue that protects the eye. It has been reported that atropine reduces the activity of the epidermal growth factor receptor in sclera fibroblasts, thereby reducing the proliferation of these cells, increasing the thickness of the scleral fibrous layer in the myopic eye, and reducing extracellular matrix production by reducing glycosaminoglycan synthesis. This can explain that myopia is prevented by suppressing the increase in the axial length of the eye. Second, atropine may affect the choroid, a layer of blood vessels that supply oxygen and nutrients to the outer retina. Originally, the choroid responds to optic defocus and controls the choroid thickness to focus. Atropine blocks the muscarine receptors of the choroid retinal pigment epithelium (RPE), modulates the transforming growth factor and basal fibroblast growth factor, and eventually suppresses choroid thinning, which is known to prevent the progression of myopia [7].

2.2 Physostigmine

In 1862, Thomas Fraser discovered the first intraocular pressure (IOP) lowering medication, physostigmine ($C_{15}H_{21}N_3O_2$), from the Calabar beans [8]. Physostigmine is a highly toxic parasympathomimetic alkaloid and a reversible cholinesterase inhibitor. After instillation into the eye, it increases the activity of free acetylcholine in the pupil sphincter, causing miosis leading to contraction of the ciliary muscle. Contraction of the ciliary muscle has been shown to decrease IOP by increasing the drainage of aqueous humor into the trabecular pathway. However, physostigmine has been replaced with safer drugs, which will be introduced below, due to side effects,

such as headache, spasm of accommodation, blurred vision due to miosis, increased risk of retinal detachment, and inflammation of the conjunctiva, cornea, and iris [9].

2.3 Pilocarpine

Pilocarpine ($C_{11}H_{16}N_2O_2$) is a cholinergic agent that was isolated by Hardy and Gerrard from *Pilocarpus* in 1875 and used as an eye drops for the treatment of glaucoma. Installation of pilocarpine reduces the size of the pupil, which can help reduce glare.

Pilocarpine is a cholinergic parasympathomimetic agent that acts through direct stimulation of muscarinic receptors and smooth muscles, such as the iris [10]. Aqueous humor is secreted from the ciliary body, travels through the pupil to the anterior chamber, and exits through the trabecular meshwork into Schlemm's canal. In angle closure glaucoma, IOP rises because aqueous flow obstruction occurs by the pupillary block. This can cause vision loss and pain in the eyeball. The therapeutic principle in angle closure is by removing the pupillary block. Pilocarpine contracts the iris sphincter muscle and pulls it away from the trabecular meshwork, widening the anterior chamber angle. As a result, it is used as an important treatment for angle closure glaucoma by resolving a pupillary block [11, 12].

Pilocarpine is also used for diagnostic purposes. Dilated pupils can appear for a variety of reasons. Among them, Adie's tonic pupil is caused by damage to the post-ganglionic parasympathetic nerve of the iris sphincter muscle. Denervation supersensitivity is a characteristic sign in Adie's tonic pupil that is confirmed by pharmacologic testing with a direct-acting weak muscarinic agonist, dilute pilocarpine [13].

Recently, pilocarpine 1.25% eye drops have been approved by the FDA for the treatment of presbyopia. Presbyopia is a condition in which near vision loss occurs due to a progressive physiological loss of accommodation. Accommodation is adjusting refraction to make focus on a near object. This can be achieved by increasing lens thickness by reducing zonular tension with ciliary muscle contraction, pupillary constriction, and convergence of both eyes. Presbyopia is known to occur due to the stiffening of the lens due to aging. About 1.25% pilocarpine is a muscarinic agent that induces miosis and ciliary body contraction and has been demonstrated to improve near vision without significantly impairing distance vision [14, 15].

2.4 Cocaine

It was first used in 1884 by Karl Köller as cocaine ($C_{17}H_{21}NO_4$) for topical ocular anesthesia. As a local anesthetic, cocaine reduces pain by blocking sodium channels in the membranes of sensory nerve endings. However, cocaine is highly toxic to corneal epithelial cells and is no longer used for anesthesia. Since then, local anesthetics for ophthalmic use have changed to tetracaine, proparacaine, and lidocaine [16, 17].

Cocaine inhibits norepinephrine reuptake and causes pupillary dilation. High concentrations can cause cycloplegia, and chronic users can cause exophthalmos and retraction of the upper eyelid [18]. Cocaine users may develop superficial punctate keratitis, epithelial defects, and ulcers through eye rubbing or retrograde passage through the nasolacrimal duct [19]. Although not directly affected by drugs, unilateral vision loss along with proptosis and ophthalmoplegia may occur due to orbital congestion and ophthalmic/central retinal artery occlusion due to continuous pressure on the orbital socket while sleeping in an abnormal posture due to unconsciousness after excessive drug abuse. Orbital congestion and proptosis improved with time, but the visual prognosis was poor [20].

2.5 Pyrrolizidine alkaloid

Heliotropium Indicum is used traditionally as a remedy for conjunctivitis. This plant is an annual, hirsute plant that is a common weed in waste places and settled areas. It is native to Asia. It is widely used in native medicine in India. The extract from the pounded leaves of this plant contains several pharmacologically active alkaloids, such as indicine ($C_{15}H_{25}NO_5$), acetyl-indicine ($C_{17}H_{27}NO_6$), indicinine-N-oxide ($C_{15}H_{25}NO_6$), heleurine ($C_{16}H_{27}NO_4$), heliotrine ($C_{16}H_{27}NO_5$), supinidine ($C_8H_{13}NO$), and lindelofidine ($C_8H_{15}NO$). These alkaloids have anti-allergic effects, possibly by immunomodulation or immunosuppression in allergic conjunctivitis. Also, this extraction exhibits an anti-inflammatory effect on uveitis, possibly by reducing the production of pro-inflammatory mediators. It was confirmed that this extract significantly reduced the concentrations of tumor necrosis factor-α (TNF-α), prostaglandin E2 (PGE2), and monocyte chemoattractant protein-1 (MCP-1) in rabbits with uveitis [21, 22].

In another study, consuming extracts of this plant could inhibit the progression of cataracts in rats. Total lens proteins glutathione and superoxide dismutase (SOD) levels in the crystalline lens were also significantly preserved. This can be the basis for a new treatment that can prevent cataract progression by suppressing oxidative stress [23]. In addition, it lowers IOP and has anti-oxidant and possible neuroprotective effects. When treated with this extract, IOP was significantly reduced in rabbits with glaucoma, and the concentration of glutathione in the aqueous humor was preserved, proving that the eyes were protected from oxidative damage. So, it has the potential to develop into a drug helpful in the treatment of glaucoma [24].

3. Various effects of alkaloids on the eyes

3.1 Caffeine

In modern society, caffeine ($C_8H_{10}N_4O_2$) is one of the most widely used dietary constituents. Caffeine is an adenosine receptor antagonist and makes a pharmacological effect on various organ systems. The lens progresses to a cataract due to the formation of reactive oxygen species (ROS) by ultraviolet light or diabetes. Caffeine has been shown to protect the lens from oxidative damage in various animal models of cataracts [25–27]. One study has shown that there is a significant negative correlation between coffee consumption and cataract incidence [28]. Given that it reduced the incidence of UV-induced cataracts in animal models, it is thought that caffeine could be an important candidate for future cataract-preventive eye drugs.

It is known that the administration of caffeine induces ocular vasoconstriction in healthy individuals. About 5% of vasoconstriction in the retinal arterioles occurred 1 hour after ingestion of 200 mg of caffeine. How caffeine induces vasoconstriction is not known in detail. Caffeine-induced vasoconstriction may represent autoregulatory myogenic smooth muscle contraction in response to elevated blood pressure. When caffeine was administered, retinal vessel diameter showed a negative correlation with mean arterial pressure, suggesting that it originates from a myogenic response [29]. Caffeine can also induce vasoconstriction by increasing sympathetic tone. Since the choroidal and ciliary circulations receive sympathetic innervation, the increased sympathetic tone may contribute to vasoconstriction of the ocular circulation [30].

Controversy has arisen about the increase in IOP after caffeine intake in normal young people, but it has been found that caffeine intake increases IOP in glaucomatous eyes [31]. Caffeine elevates IOP probably because it antagonizes the actions of adenosine, which reduces IOP. Adenosine receptors A1 and A2 are known to induce vasodilation and decrease IOP [32]. Glaucomatous eyes are known to result from damage to the aqueous humor outflow system. Several studies have shown that patients with glaucoma have abnormal vascular reactivity and peripheral microvascular circulation [33]. The action of caffeine can alter the adenosine signaling pathway, leading to differential vascular effects of caffeine in normal and glaucomatous eyes.

For a long time, studies have shown caffeine to be a potential drug for neurodegenerative diseases because of its adenosine-antagonizing properties. Since the retina is also a neurosensory organ and an extension of the brain, there is an opinion that caffeine may play a role in protecting the retina by blocking the adenosine A_{2A} receptor and controlling the reactivity of microglia [34]. In oxygen-induced retinopathy in the mouse model, caffeine intake attenuated hypoxia-induced pathologic angiogenesis and vascular occlusion without interfering with normal retinal vascular development [35]. There are suggestions that the cellular response to hypoxia is extracellular adenosine production and the markedly induced adenosine receptors, which are thought to be novel targets for pathological angiogenesis. Among them, three adenosine receptor subtypes (A_1R, $A_{2A}R$, and $A_{2B}R$) are expected to play a role [36]. Therefore, it is considered that caffeine can be an important candidate for new drugs for retinal diseases, such as diabetic retinopathy (DR), retinal vascular occlusion, retinopathy of prematurity, and age-related macular degeneration (ARMD), by using the effects of caffeine on the nerve and vascular protection.

3.2 Nicotine

Cigarette smoking is one of the most common and serious health problems today. Chemical toxicity and free radical-related oxidative damage can affect multiple structures in the body. In particular, nicotine ($C_{10}H_{14}N_2$) is known to cause changes in the conjunctival flora, irritation, redness, dry eye, ocular surface inflammation, and meibomian gland dysfunction. Tear film breakup time is known to decrease, indicating an unstable tear film. As a result, dry eye syndrome can become more severe [37–41]. Although it cannot be limited to that caused by nicotine, it is known that cigarettes have various harmful effects on the eyes. It increases the risk of squamous metaplasia of bulbar conjunctiva and conjunctival intraepithelial neoplasia [39, 42], delays corneal wound healing [43], reduces endothelial cell count or hexagonality of endothelial cells [44, 45], and can lead to cataract formation [46]. Smoking is also known to increase the risk of age-related macular degeneration [47], increase IOP [48], and induce non-arteritic anterior ischemic optic neuropathy (NAION) [49].

3.3 Opiates

Morphine ($C_{17}H_{19}NO_3$) causes miosis by acting on opioid receptors [50, 51]. The triad of coma, pupillary constriction, and depressed respiration suggests opioid addiction. Morphine abuse can cause downbeat nystagmus, transient disturbances of eye fixation, saccadic intrusions, and oscillations [52]. Intravenous abuse of this drug may cause embolization of the retinal vasculature and may result in endophthalmitis.

3.4 Quinine

Quinine ($C_{20}H_{24}N_2O_2$) was first isolated in 1820 from the bark of a cinchona tree. It has been used as a remedy for malaria since 1632. Quinine is a flavor component of tonic water and bitter lemon drink mixers. Tonic water was initially marketed as a means of delivering quinine to consumers to offer antimalarial protection. Because of the various complications of quinine and resistance to malaria, as of 2006, the World Health Organization no longer recommends it as a first-line treatment for malaria [53].

Chloroquine ($C_{18}H_{26}ClN_3$) and hydroxychloroquine ($C_{18}H_{26}ClN_3O$), derivatives of quinine, were developed and used as antimalarial drugs, but are now widely used to treat connective tissue disorders, such as systemic lupus erythematosus and rheumatoid arthritis. Retinopathy can be caused by the use of hydroxychloroquine and chloroquine, which is a serious complication. This is largely related to the dose, and it is known that the incidence of retinopathy increases when the hydroxychloroquine dose exceeds 5.0 mg/kg or the chloroquine dose exceeds 2.3 mg/kg. Although the mechanisms of chloroquine and hydroxychloroquine retinopathy have not been clarified, these drugs bind to melanin and deposit in the retinal pigment epithelium. They are thought to increase cell lysosomal pH, thereby preventing autophagosomal attachment to lysosomes, and leading to photoreceptor degradation [54].

3.5 Scopolamine

Scopolamine ($C_{17}H_{21}NO_4$) is an alkaloid used to treat motion sickness and postoperative nausea and vomiting. It was the first drug to be made commercially available in a transdermal therapeutic system delivering alkaloids. It competitively inhibits all four muscarinic receptors (M1, M2, M3, and M4) for acetylcholine and acts as a nonselective muscarinic antagonist, producing both peripheral antimuscarinic properties and central sedative, antiemetic, and amnestic effects [55]. It is used to prevent motion sickness in the form of a transdermal patch. There have been reports of mydriasis and reduced near vision occurring when rubbing the eyes with the hand that touched the patch. There are many reasons for the occurrence of mydriasis, but if there is no specific cause, contamination by scopolamine transdermal patches should also be considered [56].

It was confirmed that continuous systemic administration of scopolamine in rats could induce dry eye due to inflammation of the lacrimal gland by cholinergic blockade induced by scopolamine [57].

4. Alkaloids as candidates for new drugs in ophthalmology

4.1 Piperine

Piperine ($C_{17}H_{19}NO_3$) was discovered by Hans Christian Ørsted in 1819, and piperine was isolated from *Piper nigrum*, the source plant of both black and white pepper. Piperine is known to be able to inhibit free radicals and ROS, thereby protecting apoptotic cell death from oxidative damage. In a steroid-induced chick embryo lens model, it was confirmed that piperine exerted an effect as an antioxidant substance and prevented the development of cataracts by reducing the increase in the level of ROS [58].

The effect of piperine was also confirmed to have a protective effect on the retina in a mouse model with diabetic retinopathy. In a hypoxia-induced DR mouse model, intraperitoneal injection of piperine was found to reduce the expression of hypoxia-inducible factor-1α and vascular endothelial growth factor (VEGF) A, which are known to have an angiogenic effect [59].

4.2 Matrine

Matrine ($C_{15}H_{24}N_2O$) is an alkaloid found in *Leguminosae* plants, *including Sophora flavescens Ait*. It is known to have potent antitumor activity by inhibiting tumor cell proliferation through a variety of mechanisms, including inducing cancer cell differentiation and apoptosis, altering the tumor cell cycle, and inhibiting telomerase activity. Antitumor effects of matrine were found in vincristine-resistant retinoblastoma cells. Retinoblastoma is a malignant tumor of the retina and usually affects children under the age of 6 years. Retinoblastoma is a threat to both a child's vision and life. Treatment for retinoblastoma includes chemotherapy, radiotherapy, surgery, laser treatment, and freezing, among which vincristine is the most commonly used chemotherapy. However, resistance to chemotherapeutic agents can lead to treatment failure. When the drug-resistant retinoblastoma cell line was treated with matrine, it was confirmed that the proliferation of tumor cells was suppressed, apoptosis was suppressed, and the cell cycle was arrested. Matrine appears to induce apoptosis by downregulating the protein Bcl-2, which affects the antiapoptotic process. Matrine was also confirmed to regulate the cell cycle of tumor cells by reducing cyclin D1 expression. Matrine may be a potential treatment for vincristine-resistant retinoblastoma [60].

Matrine has been shown to inhibit optic nerve infiltration and demyelination in optic neuritis. Optic neuritis is a condition in which inflammation, demyelination, and axonal injury occur in the optic nerve, resulting in demyelination leading to temporary or permanent loss of vision. Retinal ganglion cells (RGCs) are known to undergo significant loss during apoptosis in optic neuritis. The death of RGCs has been considered the main cause of vision loss after an episode of optic neuritis. It was confirmed that matrine can promote survival by protecting RGCs from inflammation-induced apoptosis. When matrine was injected intraperitoneally in optic neuritis in the experimental autoimmune encephalomyelitis rat model, it was confirmed that the increased numbers of CD4+ T cells and Iba1+ microglia/macrophages in the optic nerves were reduced. Matrine also inhibits the production of proinflammatory cytokines, such as IFN-γ, TNF-α, and IL-17, and blocks the migration of peripheral immune cells. What causes RGCs apoptosis is a shift toward a more proapoptotic ratio in the Bcl-2 family and reduced phosphorylation of protein kinase B (Akt) proteins. Matrine is thought to protect RGCs from apoptosis by shifting the Bcl-2/Bax ratio back to an antiapoptotic one and promoting Akt phosphorylation. Matrine reduced optic nerve inflammation, demyelination, and axonal loss, and protected retinal ganglion cells from inflammation-induced cell death. Thus, matrine shows promise as a novel treatment of optic neuritis, which can lead to blindness [61].

4.3 Vincamine

Vincamine ($C_{21}H_{26}N_2O_3$) is a monoterpenoid indole alkaloid found in the Apocynaceae *Vinca* plant (lesser periwinkle). It is used as a treatment for primary degenerative and vascular dementia. It can improve the metabolism of ischemic tissue

and protect the neuron. A recent study demonstrated that vincamine has a potential neuroprotection effect in NAION. Vincamine can rescue the death of retinal ganglion cells and reduce the number of apoptotic cells. The protection of vincamine might play through the phosphoinositide 3-kinases (PI3K)/Akt/endothelial nitric oxide synthase (eNOS) signaling pathway. Therefore, vincamine can be an effective therapy method NAION [62].

4.4 Papaverine

Papaverine ($C_{20}H_{21}NO_4$) was discovered in 1848 by Georg Merck. Papaverine is a nonselective phosphodiesterase inhibitor and is mainly used for cerebral thrombosis, pulmonary embolism, and arterial spasms by relaxing cardiovascular, respiratory, and gastrointestinal smooth muscles. Recent studies have confirmed evidence that papaverine can protect the optic nerve. Cyclic adenosine 3,5′-monophosphate (cAMP) is known to play an important role in ATP metabolism. It is known that the exogenous addition of cAMP increases the content of synaptic binding protein in axons, promotes the survival of neurons and outgrowth of axons due to nerve injury, and accelerates functional recovery of the central nervous system. Intracellular cAMP levels are regulated by the activity of phosphodiesterase, and phosphodiesterase inhibitors increase cAMP levels by inhibiting the hydrolysis of cAMP. Papaverine regulates the expression of cAMP by inhibiting lipopolysaccharide-induced retinal microglial activation, which plays a role in phagocytosis and secretion of inflammatory mediators by regulating the nuclear factor-kB (NF- kB) and mitogen-activated protein kinase (MEK) /extracellular signal-regulated kinases (ERK) pathways. This was eventually confirmed to induce axonal regeneration of RGCs. This showed potential as a treatment for optic nerve damage, such as glaucoma [63–65].

4.5 Berberine

Berberine ($C_{20}H_{18}NO_4^+$) is a natural bioactive alkaloid derived from a variety of Chinese Medicinal herbs, including *Rhizoma Coptidis*. It has been reported with various pharmacological effects, such as anti-inflammation, anti-oxidation, hepatic protection, and anticancer. In a recent study, berberine was found to be effective in insulin-induced diabetic retinopathy. When Akt/mTOR signaling is activated by insulin, the risk of neovascularization in the retina of diabetic animals may increase due to an increase in hypoxia-inducible factor-1α (HIF-1α)/VEGF in retinal endothelial cells. When insulin-induced neovasculature of retina endothelial cells was treated with berberine, it was found to improve insulin-induced DR by inhibiting Akt/mammalian target of rapamycin (mTOR) activity and reducing the expression of the HIF-1α/VEGF pathway [66].

In addition, studies have shown that berberine can protect the retina from light-induced photoreceptor degeneration. In the light-damaged retina, RPE65 and Mct3 proteins were down-regulated, resulting in photoreceptor damage. It has been shown that the PI3K/AKT/ERK pathway plays a major role in ultraviolet-induced RPE damage. The mice treated with berberine had more photoreceptor nuclei in the outer retina and photoreceptor inner/outer segments and higher RPE65 and Mct3 in the RPE than the control group. Berberine was found to protect against light-induced retinal damage by activating the PI3K/AKT/ERK pathway. This can be considered to show the potential of a drug that can protect photoreceptors from ARMD [67].

4.6 Sanguinarine

Sanguinarine ($C_{20}H_{14}NO_4$) is a type of benzophenanthridine alkaloid extracted from the root of the herbaceous plant *Sanguinaria canadensis*. It is known to have antimicrobial, anti-inflammatory, anti-oxidative, and tumor-suppressing properties. Sanguinarine has been found to be effective in preventing after-cataracts. After-cataract refers to the posterior capsule opacification that occurs after cataract surgery and is caused by the regeneration of residual lens epithelial cells. Sanguinarine significantly reduced the viability of human lens epithelial B-3 cells and induced apoptosis. Apoptotic effects probably induce reactive oxygen species generation and promote phosphorylation of c-Jun N-terminal kinase (JNK) and p38 kinases, suggesting that the mitogen-activated protein Kinase (MAPK) pathway is involved in apoptosis. Sanguinarine may be used as a potential drug for after-cataract prevention [68].

Sanguinarine has been shown to have antiangiogenic effects in wet ARMD. A major feature of wet ARMD is choroidal neovascularization, in which pathological neovascularization originating from the choriocapillaris breaks through Bruch's membrane and creates leakage in the subretinal space, resulting in reduced visual acuity. The treatment of wet ARMD is to suppress angiogenesis by administering intravitreal injections of antibodies against VEGF. Intravitreal injection of sanguinarine chloride was performed in the choroidal neovascularization mouse model, and as a result, the formation of choroidal neovascularization was suppressed and the expression of VEGF was reduced. Sanguinarine inhibited VEGF-induced AKT, ERK, and MAPK signaling pathways. Sanguinarine has been suggested as a potential treatment for wet ARMD [69].

4.7 Galantamine

Galantamine ($C_{17}H_{21}NO_3$) is an alkaloid used as a treatment for Alzheimer's disease, a cognitive disorder. These are the bulbs and flowers of *Galanthus nivalis* (Common snowdrop), *Galanthus caucasicus* (Caucasian snowdrop), *Galanthus woronowii* (Voronov's snowdrop), and some other members of the family *Amaryllidaceae*, such as *Narcissus* (daffodil), *Leucojum aestivum* (snowflake), and *Lycoris,* including *Lycoris radiata* (red spider lily). Galantamine acts as an acetylcholinesterase inhibitor and an allosteric ligand of nicotinic acetylcholine receptors. Recent studies have shown that it also has neuroprotective effects. In one study, galantamine was found to promote the protection of RGCs in a rat glaucoma model. Galantamine-induced ganglion cell survival was caused by the activation of types M1 and M4 muscarinic acetylcholine receptors. This showed the potential of galantamine as a neuroprotectant for glaucoma [70]. A further study by the same authors confirmed that galantamine preserved microvasculature density and improved retinal blood flow in the glaucomatous retina, strengthening the evidence for its neuroprotective effect in glaucoma [71].

5. Conclusions

Since ancient times, alkaloids have been extracted from natural substances and have various effects on the eyes. Several alkaloids have been used medicinally since that time. Atropine induces mydriasis and has been used for diagnosis and treatment. Physostigmine and pilocarpine were first used as treatments for glaucoma because they constrict the pupil and reduce IOP. Cocaine was used as an ophthalmic anesthetic but is not currently used due to toxicity. However, there are cases where

existing alkaloids are used for new purposes. Recently, atropine has attracted attention as a therapeutic agent that inhibits myopic progression, and pilocarpine has been recognized and used as a treatment for presbyopia.

Alkaloids also had various effects. Caffeine inhibits cataract progression from oxidative damage and reduces hypoxia-induced angiogenesis, but is known to induce an increase in IOP. Nicotine is known to aggravate dry eye syndrome and blepharitis by influencing the ocular surface and to induce the formation of conjunctival tumors and cataracts. Chloroquine and hydroxychloroquine, derivatives of quinine, are drugs widely used in rheumatic diseases, but can cause retinopathy.

Finally, alkaloids are being studied in some studies as new drugs in the field of ophthalmology. Matrine, vincamine, papaverine, and galantamine were newly found to be able to protect the optic nerve, confirming the possibility of developing a treatment for diseases, such as glaucoma or optic neuropathy. In addition, piperine and sanguinarine have been found to be associated with the formation of cataracts. Matrine is expected to be effective in treating vincristine-resistant retinoblastoma. Piperine, berberine, and sanguinarine are expected to be helpful in treating diseases related to retinal neovascularization. They are expected to become therapeutic agents for various ophthalmic diseases in the future.

Conflict of interest

The authors declare no conflict of interest.

Acronyms and abbreviations

RPE	Retinal pigment epithelium
IOP	intraocular pressure
TNF-α	tumor necrosis factor-α
PGE2	prostaglandin E2
MCP-1	monocyte chemoattractant protein-1
SOD	superoxide dismutase
ROS	reactive oxygen species
DR	diabetic retinopathy
ARMD	age-related macular degeneration
NAION	non-arteritic anterior ischemic optic neuropathy
VEGF	vascular endothelial growth factor
RGCs	Retinal ganglion cells
Akt	protein kinase B
PI3K	phosphoinositide 3-kinases
eNOS	endothelial Nitric Oxide Synthase
cAMP	cyclic adenosine 3,5'-monophosphate
NF- kB	nuclear factor-kB
MEK	mitogen-activated protein kinase
ERK	extracellular signal-regulated kinases
HIF-1α	hypoxia-inducible factor-1α
mTOR	mammalian target of rapamycin
JNK	c-Jun N-terminal kinase
MAPK	mitogen-activated protein Kinase

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