Chapter 1
Ocular Pharmacology and Therapeutics: Origin, Principle, Challenges, and Practices

Thirumurthy Velpandian and Suresh Kumar Gupta

Abstract Recent revelations on the origin of eye specific applications bring out the fascinating history from various civilizations. Use of black kohl eyeliner and the possible science behind it has been explored through contemporary technology. Chemical analysis of the contents of the pyxis recovered from the Roman vessel that was shipwrecked off the coast of Tuscany more than 2000 years ago, showed the presence of higher amounts of zinc which might have been used to treat eye infections. Literatures available from ancient civilizations indicate the use of many INTERESTING drug formulations for the eye. This chapter narrates the history for such usage attributing to the development of medications for ocular therapeutics, principles of ocular therapy and challenges in applying ocular pharmacology to therapeutics.

1.1 Origin of Eye Medications in the Human History

Almost in all ancient civilizations, the eye and vision had a special place in their evolution. Eye paint was used as a remedy to strive against evil spirits entering through nine vulnerable openings in the body in ancient Mesopotamia. The importance of ophthalmic ointments and eye paint was particularly signified in the Egyptian culture. The importance of the eye was immortalized through the myth of the Eye of Horus which says that one eye represents the moonlight while the other

T. Velpandian, BPharm, MS(Pharmacol), PhD (✉)
Ocular Pharmacology and Pharmacy, Dr. Rajendra Prasad Centre for Ophthalmic Sciences, All India Institute of Medical Sciences, New Delhi 110 029, India
e-mail: tvelpandian@hotmail.com

S.K. Gupta, PhD, DSc, FIPS, FIACS
Pharmacology/Clinical Research, Delhi Institute of Pharmaceutical Sciences and Research (DIPSAR), University of Delhi, New Delhi, India

Research (DIPSAR), University of Delhi, New Delhi, India

T. Velpandian (ed.), *Pharmacology of Ocular Therapeutics*,
DOI 10.1007/978-3-319-25498-2_1

eye represents the sunshine. The two eyes altogether thus represent the power of human intellect. Blindness, in turn, was seen as a divine punishment. To protect the eyes from blindness, Egyptians used to apply drops and ointments, to chase away insects and demons that were associated with a variety of eye infections.

The Egyptian physicians for eye diseases carried a special kit that contained a black kohl make up and green chrysocolla. Kohl served multiple roles in the Egyptian culture. Moreover, the Egyptian of all social classes smeared their eyelids with black kohl eyeliner in veneration of the deities. Kohl also signified one's status in the society with the glossiest, highest-quality kohl denoting one's upper class status in society while the less wealthy applied kohl of fire soot. Kohl applied liberally around the eyes helped to reduce the sun's glare, to repel flies, and to provide cooling relief from the heat. It also trapped errant dust and dirt common in the desert.

The typical composition of kohl which was used in Egypt in the recent past has been reported to contain crushed stibnite, burnt almonds, lead, oxidized copper, ochre, ash, malachite, and chrysocolla (Murube 2013), whereas the original composition of kohl used in ancient Egypt is now known from the work of French researchers reported in 2010. They have analyzed 52 kohl samples from the Egyptian make up containers residing at the Louvre museum in Paris. The research of their study reported the presence of trace amounts of four uncommon lead species: galena (PbS), cerussite (PbCO3), phosgenite (Pb2Cl2CO3), and laurionite (Pb(OH)Cl) in the cosmetics (Tapsoba et al. 2010).

Kohl was predominantly composed of the mineral galena, a dark, metallic lead-based product that is also known by the chemical name lead sulfide (PbS). The minerals were further reported to be crushed and mixed with several other ingredients such as ground pearls, rubies and emeralds, silver and gold leaves, frankincense, coral, and medicinal herbs such as saffron, fennel, and neem . The resulting formulation was then diluted in liquids such as oil, gum, animal fats, milk, or water to solubilize the lead and assist in its eventual facial smearing. Thus the composition of kohl made authors of the study to quote that "it is clear that such intentional production remains the first known example of a large scale chemical process" (BMJ 1909).

When researchers exposed skin cells to the lead sulfates found in kohl, they discovered that the lead ions elicited a profound immunological response. The cultured cells released one of the most important messenger molecule in the immune system, nitric oxide gas (NO); this gaseous molecule serves as an activating messenger to bacteria-eating macrophage cells and stimulates blood flow by increasing the diameter of capillaries, encouraging rapid immune cell movement within the bloodstream. The abovementioned molecular interaction of kohl illustrates its role not only as a beautifying cosmetic but also an antibacterial ointment. As eye infections would have been a common problem in tropical marshy places such as Nile area, application of kohl must have played a prominent role in the Egyptian custom (Tapsoba et al. 2010).

In death, pouches containing kohl were buried alongside the departed, illustrating its indispensable role in the Egyptian traditions. Kohl also observes a mention in the Egyptian manuscript – Ebers papyrus, the oldest known medical texts in existence. In the hieroglyphic manuscript dating from 1550 BC, Egyptians mention detailed herbal preparations for eyedrops, salves, and ointments. However, an old Babylonian tablet (16–20 century BC) from Nippur showing medication for various parts of the body is the oldest known prescription of an ointment for eyes (BAM IV

393). Neo-Babylonian tablets (5–6 century BC) dealing exclusively with eye diseases have been discovered. These contain prescriptions of ointments for eyes. The individual instructions begin with a list of ingredients and end with the conditions for which the ointment has to be used (BAM IV 383, Attia and Buisson 2006).

Apart from the ores of lead in the kohl, the use of zinc in ocular medication was well documented in one of Galen's treatises, Medicines according to Places.

> Cleaned Cadmia (zinc oxide), 28 drams; hematite stone, burnt and washed, 24 drams; Cyprian ash (i.e. copper), 24 drams; myrrh, 48 drams; saffron, 4 drams; Spanish opium-poppy, 8 drams; white pepper, 30 grains; gum, 6 drams; dilute with Italian wine. Use with an egg **(Galen, Compositions of medicines according to places 4.8, 12.774 Khun)**

This timeless application of zinc in ocular medication came from a breaking finding in the history of medicine which came to light in the year 2013 with the findings from the analysis of the contents of a shipwreck Relitto del Pozzino dated 140–130 BCE. The vessel was laying about 18 m underwater in the Baratti Gulf, not far from the remains of the important Etruscan city of Populonia, a key port along trade routes across the Mediterranean. It was thought to be a trading ship sailing from the Asia Minor and Greece areas, carrying wine, glass cup, and lamps off the coast of Tuscany near Etruscan town of Populonia in Italy (Fig. 1.1).

The boat was found to have various pharmacological preparations along with a surgery hook, a mortar 136 wooden drug vials, and in particular several tin boxes (pyxides) (Fig. 1.2). X-ray examination of the tin boxes revealed the presence of well-preserved circular tablets in dry form even after resting in the seafloor for such a long time of 2000 years. Interestingly, five grey disc-shaped tablets enclosed in the watertight tin pyxis lying on the seabed of the Baratti Gulf wrapped in dense marine flora revealed a rare archaeological finding about the medicine used 2120 years before (Fig. 1.3).

Fig. 1.1 Picture showing boxwoods recovered from the shipwrecked Relitto del Pozzino can be seen on display at the Archaeological Museum of Populonia in Piombino, Italy

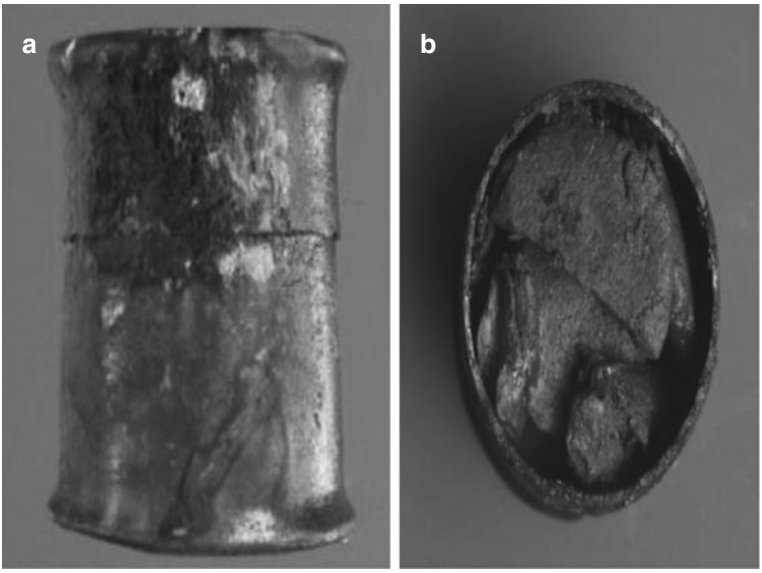

Fig. 1.2 Airtight tin container kept in a boxwood stored aboard of a Roman vessel that was shipwrecked off the coast of Tuscany more than 2,000 year ago. The A/6 pyxis before it was opened (**a**) and the pyxis showing it content (**b**) (Gianna et al. 2013; reproduced with permission)

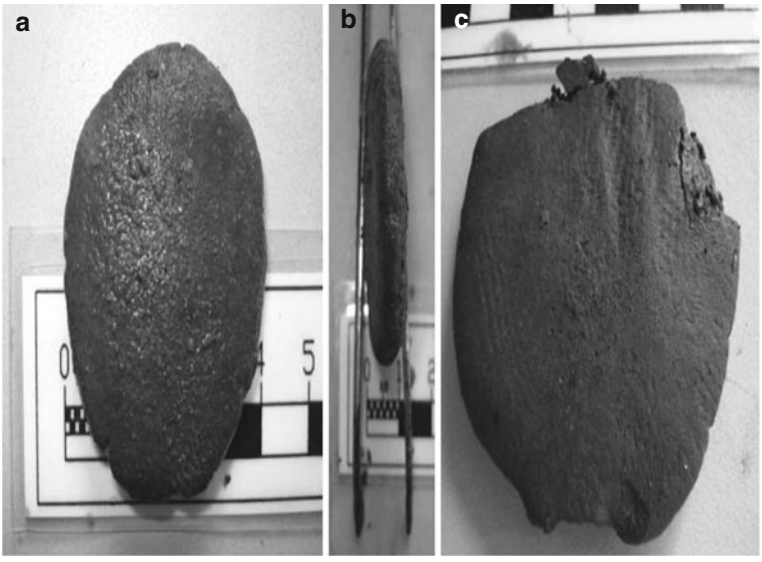

Fig. 1.3 Picture showing grey tablets, each about the shape of a circular makeup sponge, inside an airtight tin container stored aboard a Roman vessel that was shipwrecked off the coast of Tuscany more than 2,000 year ago. (**a**) The Front (**b**) side & (**c**) back view profile of tablet found in the A/6 pyxis (Giachi et al. 2013 reproduced with permission). *Note*: chemical analyses revealed the presence of starch, pine resin, beeswax, and fats in the ancient drugs, with higher amount of zinc compounds indicating that it might have been used to treat eye infections

Subjecting them for chemical analysis using advanced analytical instruments revealed extraordinary information on the composition of the tablets and on their possible therapeutic use. Hydrozincite (zinc hydroxycarbonate) and smithsonite (zinc carbonate) were two of the most abundant ingredients of the Pozzino tablets, along with starch, animal and plant lipids, and pine resin. From the composition, the authors reached a conclusion that the Pozzino tablets were used for ophthalmic purposes.

Concurrently Roman oculist stamps demonstrate a classification of ocular disease, a system of treatment, and reveal the names of practitioners (Marmion 1995). Roman oculist stamps were associated with collyria, and collyrium stamps are parallelepipedic stones that were used in the Roman world, between the second part of the first century and the fourth century A.D., to stamp eye medicine (Perez-Cambrodi et al. 2013). The Latin expression collyrium (eyewash) comes from the Greek name κο λλυ′ ρα, which means "small round loaves" (Giachi et al. 2013). These seals specifically those of Roman eye medicine were inscribed according to the Greek medical tradition indicating the name of the patient, therapeutic instructions, method of administration, etc. Thus, the Greek medical texts reveal the influence of the Greek ophthalmology on Roman eye medicine (Pardon-Labonnelie 2014). Collyrium also refers to the composition of powders brought to a pasty consistence with a liquid and formed into tentlike structure for insertion into (Murube J, 2007a).

Another usage of the vocabulary of collyrium refers to Keshanjana (collyrium), an Ayurvedic formulation prepared out of Keshamasi (ash prepared by scalp hairs) mixed with Goghrita (cow ghee). This particular preparation is indicated for treating Chushkashipaka (dry eye syndrome) in Vagbhatta Samhitas and classical Ayurvedic treatises (Kartar et al. 2014). Ayurvedic and Siddha medical systems originated from different parts of India reported several medicines for ocular use (Subbarayappa 1997; Ven Murthy et al. 2010). Ayurveda dates back to the Vedic period of the Indus Valley Civilization (about 3000 BC) and has been passed on through generations of oral tradition, like the other four sacred texts (Rigveda, Yajurveda, Samaveda, and Atharvanaveda) which were composed between the twelfth and seventh century BC (Ven Murthy et al. 2010).

In the ancient Indian Ayurvedic texts, Shalakya tantra is referred as one among Ashtang Ayurveda (eight super specialities) specifically for the diagnosis, treatment, and prevention of all the diseases occurring above the neck such as eyes, nose, ear, mouth, and head. According to the Vedic scripts, the father of Shalakya tantra was referred as King Nimi (king of Videha). Among the eight super speciality disciplines, Netra Chikitsa is considered as referring to the treatment for ocular diseases.

Anjanam is an ancient Ayurvedic eyeliner and paint explained for cleansing and therapeutic purposes (Fig. 1.4). Although it has been known to exist in the ancient Ayurvedic literature, its relevance to the origin of its use has not been studied systematically. Although the effects of plants with psychoactive substances have been manifested in many ways, one account in Indian Ayurvedic literature details about the use of Datura. "Harita Samhita" explains, Datura root is crushed in water and strained liquid is used in instilling in sore eyes (conjunctivitis). Cannabis extract was used for sore eyes by the Egyptians around 2000 BC (Webley K 2010). They have also used squill for dropsy under the mystic name of the "Eye of Typhon."

Fig. 1.4 The tenth century carving on stone at Parshvanath temple, Madhya Pradesh, India, showing an *Apsaras* (angel) applying kajal (collyrium)

Chinese philosopher Mo-Zi (fifth to fourth century BC), recorded the effects of pharmaceutical substances on the quality of eyes "there is a drug for this. if one eats it, the eye will become sharp and the eye will be clear.". However, the Wan wu text among the Fu-yang bamboo manuscripts found in the tomb of Xiahou Zao, the Lord of Ruyin who died in 165 BC, quotes the recommendation "Ox gall brightens the eye so that one may climb on high on slip thirty-five" (Shaughnessy 2014).

In a Celtic leech-book preserved in the University of Leyden (nineteenth century), shows the treatment for the dimness for eyes. One of the formulations contained pound fennel roots, mixed with honey and boiled over slow fire, with cistern water or woman's milk and smearing eyes with the fat of a fox (Adipe vulpis). Another remedy claims a mixture of a child's urine (lotium infantis) with the best honey; add a decoction of fennel roots (Thompson 1897).

An excellent recipe for sore eyes was the juice of the calyx of the red honeysuckle prescribed in 1553. The flowers had to have been gathered kneeling and

repeating nine Paternosters in honor of the Trinity, nine more "to greet our Ladye," and a creed. The abovementioned My Ladye Falkenbrydge's recipe for eyewater was thus much esteemed and ran as: "Corne-flowers gathered with their cuppes and bruyse them; macerate them in snow or snow water for twenty-four hours, then dystyl in a moderate sandebath and applye it night and morning" (Thompson 1897).

Interestingly the old apothecary's prescriptions in 1685 were composed of strange ingredients, including crab's eyes and boar's teeth, or powdered pearls, and viper broth (Thompson 1897).

At the same time, eyedrops were also used miraculously to cure dental pain. A writer of the Time states that the itinerant dentist was also a well-known figure at the street corner. For 100 marks, he would put out both your eyes and quite cure your inflammation with one drop of his aqua mirabilis, at 12 pence a drop (fifteenth century).

Over a period of centuries, eye diseases were not classified; especially the two major problems were not clearly differentiated. It is somewhere in 1820 that a clear differentiation between glaucoma and cataract was seen in the history. The earliest understanding towards the usage of any substance having a meaningful ocular use come from the observations of the Greek women. The Greek women used the juice of the berries of *Atropa belladonna* to enlarge their pupils for cosmetic reasons. In Italy belladonna refers to "beautiful lady." The alluring beauty of Queen Cleopatra of the last century BCE has been attributed to her dilated pupils by using the extracts from the Egyptian henbane (*Hyoscyamus niger*). Friedlieb Ferdinand Runge, a German chemist, demonstrated the mydriatic effect of the extract of the deadly nightshade in 1819. Atropine in its crystalline form was isolated in 1831 by the German pharmacist Heinrich F. G. Mein. However, atropine has been used for more than a century now by ophthalmologists throughout the world for dilating iris.

It is interesting to know that the knowledge about the dilation property of belladonna was existing for long among the Greek women for making themselves attractive. The same practice has been continued even today when modern photographers use the same technique to make female portraits with attractive eyes. Discovery of contact lenses make this practice in modern times more comfortable by largely using cosmetic contact lenses to give the illusion of dilated eyes. The rationale for the hypothesis came from the investigations of Tombs and Silverma (2004) that the reproductive strategies of males are best served by unequivocal female sexual interest and arousal indicated by dilated pupils (Tombs and and Silverma 2004).

Pilocarpine preparations have been used since 1870s with their first record starting in the mid-nineteenth century. During that time, European visitors to Old Calabar, an eastern province of Nigeria and Africa, came to know about the native belief in the power of the seeds of a local plant to determine whether individuals were innocent or guilty of misdemeanor. Missionaries who arrived in Calabar in 1846 realized that the particular bean was responsible for more than 120 deaths annually. This information rapidly reached Scotland, the home of the missionaries' parent church for evaluation. Slowly, exploration of the bean started and reached a stage when Balfour's comprehensive botanical description of the bean plant appeared as *Physostigma venenosum*. In 1863 a young Edinburgh ophthalmologist, Argyll Robertson, published a paper announcing the arrival of the first agent that constricted the pupil of the eye (Proudfoot 2006).

The drug was an extract of Calabar beans, and Argyll Robertson openly admitted that he had been alerted to its unusual property by his physician friend, Thomas Fraser. Later Fraser extensively studied the action of Calabar bean on the eye and noted down its opposing action to atropine. However, in 1864, an ophthalmologist, Niemetschek, working in Prague in 1864 recommended Calabar bean extract to his friend Kleinwächter who was treating a young man with atropine intoxication (Nickalls and Rudorfer 1980). This rendered the patient to survive atropine toxicity and incidence establishing the beans antagonism of atropine. In 1870 Fraser reported his firm belief that physostigmine and atropine were mutually antagonistic at a physiological level and opened a new era in cholinergic system for further careful interpretations (Proudfoot 2006). The modern understanding about glaucoma pharmacology began in 1862 along with the isolation of physostigmine from the Calabar bean. The discovery of epinephrine's intraocular pressure-lowering capacity came along some 40 years later (Realini 2011). In the twentieth century, ocular drug development took an advanced pace along with the rapid development of drugs for cardiovascular and central nervous system disorders (Table 1.1).

The need to administer pilocarpine frequently everyday has been unfavorable for many glaucoma patients. In the 1980s, beta-blockers were developed, reducing the administration frequency to twice a day. In 1999, prostaglandin-type ophthalmic preparations that require a once-a-day administration appeared on the market, easing the burden of frequent administration. During the process of the development of these new ophthalmic agents, Ocusert, a sustained-release pilocarpine preparation that is inserted into pre-corneal area only once a week, was designed and applied clinically (Komatsu 2007).

In modern ocular therapeutics, several plant-derived products like *Atropa belladonna* (Atropine), Datura specs (tropane alkaloids), *Physostigma venenosum* (physostigmine), *Pilocarpus jaborandi* (pilocarpine), *Ephedra* (ephedrine), and *Cannabis sativa* (cannabis) were identified and reported to have some relevance directly or indirectly to various ocular conditions. Interestingly, they are being used in its original form; their semisynthetic derivatives are having a strong holding in the modern ophthalmic practice for either therapeutic or diagnostic purposes.

Table 1.1 Significant milestones in the development of drugs for ocular therapeutics

1831	Atropine isolated in crystalline form
1870	Physostigmine isolated
1875	Pilocarpine isolated
1885	Effect of pilocarpine on IOP recorded
1920	Nonselective sympathomimetics (epinephrine and dipivefrin)
1950	Oral carbonic anhydrase inhibitors (acetazolamide)
1970	Beta-blockers (timolol, levobunolol)
1990	Topical carbonic anhydrase inhibitors, fluoroquinolones antibacterial photodynamic therapy
2000	Intraocular antiangiogenic agents (ranibizumab, bevacizumab, pegaptanib)

1.2 Principles of Ocular Therapy

After the Second World War, sterility of drug for eye has been recognized as a mandate for topical eyedrops. Usage of preservatives came into picture to avoid bacterial contamination or growth in the multi-dose eyedrop vial for their use up to 30 days after opening. However, few fundamental aspects need emphasis while administering them to the patients or self-administration. One need to remember the appropriate way of application of an eyedrop (Table. 1.2). Most of the eyedrops are clear-colored or colorless solutions with or without preservatives, iso-osmotic and buffered to have neutral pH, with exception in suspensions like prednisolone acetate, dexamethasone, basifloxacin, etc. Application of eyedrops with lesser volume (drop size) or single drop is known to have better ocular bioavailability as compared to larger volume or multiple drops.

Cornea is a specialized tissue, devoid of blood vessels having hydrophobic epithelium followed by hydrophilic stroma thereby restricting the entry of both hydrophobic and hydrophilic compounds for gaining access to aqueous humor. Cornea is highly sensitive for pH of the ingredients, osmolarity (hypo and hyper), nonspecific irritants, and pH of the formulations. The pH and nonspecific irritation can induce reflux tearing which in turn washes away the pre-corneal drugs. Predominately, drugs applied topically take transcellular diffusion pathway as corneal epithelium is reported to have tight intracellular junctions (zona occludens); therefore, less than 5 % of the topically applied drug dosage reaches aqueous humor. As less amount of drug reaches into aqueous humor, conventionally, drug concentrations are increased considerably in the applied drops to reach adequate levels for the pharmacological activity.

However, the modern understanding for the transfer of drugs across cornea is explained much better by the presence of drug transporter proteins in corneal epithelium and endothelium. These transporters are physiologically responsible for the

Table 1.2 How to apply eyedrops

Clean hands with soap solution and dry it
Open the dropper cap
Do not touch the tip of the dropper
Slightly tilt the head backwards
Gently pull the lower eyelid with one hand
Place only one drop of the drug solution into the lower fornix (do not apply two drops)
Close the eyes and sit quietly for 1 min
If possible apply a gentle pressure on the tear duct by pressing near medical canthus with index finger for a while – this will avoid the immediate entry of drug solution into the lacrimal drainage system
If two different drops need to administered, it should be done by with the interval of at least 15 min between them
Close the eyedropper without touching the dropper tip and store it in a cool and dry place
Unpreserved eyedrops must be kept in refrigerator at 2–6 °C

uptake of nutrients for the survival of cornea and to maintain its transparency by regulating its homeostasis. Systemically, administered drug seldom reaches adequate concentration into the tissues of the eye with the considerable concentration for expected pharmacological action. Most of the systemically administered antibiotics were reported to fail to reach adequate concentration due to the presence of blood-ocular barriers (Velpandian 2009).

Therefore, selecting appropriate route of drug administration to the eye is expected to having better pharmacodynamic profiles. Based on requirement, subtenon, retrobulbar, subconjunctival, intracameral, intravitreal, and peribulbar routes are preferred to comply required drug concentration at a particular site in the eye.

1.3 Challenges in Ocular Therapeutics

Ocular therapeutics is the only area in which the drugs used more than 100 years ago are still having its presence in clinical practice. Despite the multidimensional drug development approaches of the contemporary period, it is rare to see any specific agent being developed for ocular use considering the penetration constraints exerted by the eye after topical or systemic administration. Most of the drugs, approved for systemic use, are often exploited for ocular use without rationalizing the penetration characteristics in the drug development stage. Lack of considerable market size for drugs other than for glaucoma and retinal neovascular conditions could have been the major limiting factor for not getting much of industrial emphasis for ocular-specific drug discovery. Due to the application of modern techniques on traditional knowledge, ocular applications of herbal drugs are continuously increasing. However, in most of the cases, there are isolated publications on animal models or human studies which are not having any big impact for their wider use in ocular therapeutics. Therefore, developing drug specific for the eye with the consideration of its constraints would be beneficial for the further development of ocular pharmacology and its application to therapeutics.

1.4 Ocular Pharmacology and Its Practice

Ocular applications of many drugs are due to their mutual borrowings from several fields of medicine. However, all of them may not been approved for its ocular use due to the lack of initiation for the application to the regulatory authorities for their use in ophthalmology. Off-label use of drugs is commonly evident in ophthalmology; therefore, requirement of a compounding pharmacy in the final translation of drugs approved for other systemic use for ocular therapeutics. One of the chapters in this book deals with extensively about this aspect in detail. Along with the increasing knowledge about the pathology of ocular disease, we are sure that usage of extemporaneously prepared drugs might increase further in the future. During such attempts, a rational approach is expected to justify their appropriate usage in ocular therapeutics.

References

BMJ. The ophthalmology of the pharaohs. BMJ. 1909;2(2543):902.
Giachi G, et al. Ingredients of a 2,000-y-old medicine revealed by chemical, mineralogical, and botanical investigations. Proc Natl Acad Sci U S A. 2013;110(4):v1193–6.
Jeanette CF. Cuneiform tablets on eye diseases. In: Attia A, Buisson G, editors, Mesopotamian medicine from hammurabi to hippocrates. Proceedings of the International Conference "Oeil malade et mauvais oeil," Collège de France, Paris, 23rd June 2006 published by Brill, Boston; 2009.
Kartar SD, Kartar JS, Nayan RB, Vinay RS. Quality control evaluation of Keshamasi, Keshanjana and Keshamasi eye ointment. Ayu. 2014;35(1):58–62.
Komatsu Y. A history of the development of eye drops used to treat glaucoma. Yakushigaku Zasshi. 2007;42(1):7–16. Japanese. PubMed.
Marmion VJ. The Roman oculist stamps. Bull Soc Belge Ophtalmol. 1995;259:215–7.
Murube J. Collyrium: where does this word come from? Ocul Surf. 2007a;5(4):264–8. PubMed.
Murube J. Hunain's eye: the oldest preserved scientific image of the ocular surface. Ocul Surf. 2007b;5(3):207–12. PubMed.
Murube J. Ocular cosmetics in ancient times. Ocul Surf. 2013;11(1):2–7.
Nickalls RWD and Rudorfer MV. Physostigmine for anticholinergic drug poisoning. 1980; 316 (8194):589–90.
Pardon-Labonnelie M. Collyrium names attested on stone tablets: the example of the Helvetian corpus. Stud Anc Med. 2014;42:240–55. PubMed.
Perez-Cambrodi RJ, Pinero DP, Mavrou A, Cervino A, Brautaset R, Murube del Castillo J. Collyria seals in the Roman Empire. Acta Med Hist Adriat. 2013;11(1):89–100.
Proudfoot A. The early toxicology of physostigmine: a tale of beans, great men and egos. Toxicol Rev. 2006;25(2):99–138.
Realini T. A history of glaucoma pharmacology. Optom Vis Sci. 2011;88(1):36–8.
Shaughnessy EL. Recently discovered manuscripts of the Yi Jing (I Ching) and related texts. New York: Columbia University Press; 2014.
Subbarayappa BV. Siddha medicine: an overview. Lancet. 1997;350(20/27):1843–4.
Tapsoba I, Arbault S, Walter P, Amatore C. Finding out egyptian gods' secret using analytical chemistry: biomedical properties of egyptian black makeup revealed by amperometry at single cells. Anal Chem. 2010;82(2):457–60.
Thompson CJS. The mystery and romance of alchemy and pharmacy. London: The Scientific Press Ltd. 1897, XIX. p. 97.
Tombs S, Silverma I. Pupillometry: a sexual selection approach. Evol Hum Behav. 2004; 25(4):221–8.
Ven Murthy MR, Ranjekar PK, Ramassamy C, Deshpande M. Scientific basis for the use of Indian ayurvedic medicinal plants in the treatment of neurodegenerative disorders: ashwagandha. Cent Nerv Syst Agents Med Chem. 2010;10(3):238–46.
Velpandian T. Intraocular penetration of antimicrobial agents in ophthalmic infections and drug delivery strategies. Expert Opin Drug Deliv. 2009 Mar;6(3):255–70.
Webley K. Brief history: medical marijuana. Time, 21 June 2010.
Zeitschrift für celtische Philologie (ZcP). 1(1): Pages 17–25, ISSN (Online) 1865-889X, ISSN (Print) 0084-5302, DOI: 10.1515/zcph.1897.1.1.17, October 2009.