IJPSR (2014), Vol. 5, Issue 12 **(Review Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 22 April, 2014; received in revised form, 21 June, 2014; accepted, 08 August, 2014; published 01 December, 2014

A REVIEW ON AYURVEDIC MEDICINAL PLANTS FOR EYE DISORDERS FROM ANCIENT TO MODERN ERA

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Keywords:

Ayurveda, *Sushrut Samhita*, conventional drugs, eye disorders

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ABSTRACT: The management of eye disorders by chemical drugs without any side effects is still a challenge to the medical system. But the herbal medicines have potential to overcome the limitations associated with conventional drugs. Therefore; many efforts have been made to identify new medicinal plants from different sources because of their effectiveness, fewer side effects and relatively low cost. Approximately 200 plants worldwide have been documented to support treatment of eye disorders and several plant species have been advocated in Traditional Indian Medicine for their ophthalmic effects. In the present review it is proposed to highlight the medicinal plants used from ancient time for the treatment of eye diseases, their merits and demerits and role of Modern medicines over demerits of medicinal plants traditionally used for eye disorders. Review concluded that by using techniques and polymers of modern era, the best Ayurvedic formulations may be developed.

INTRODUCTION: In the Ayurvedic system of medicine, as mentioned in ancient Indian books like *Charak Samhita*, *Sushrut Samhita*, *Bhav prakasha*, *Ras Tarang*, Nayan Drastam and *Astanghriday*, there are a number of plants which are used in ophthalmic disorders, either single or in compound formulations. In Ayurveda (Indian system of medicine) various eye disorders and diseases like *Abhishyand* (Conjunctivitis), *Adhimanth* (Glaucoma), *Timir* (Cataract), etc. have been described in great details[1]. Their etiology and treatments have also been described. Various herbal drugs in different dosage forms like extract, *arkas* (aqueous distillate), *kajal* (collerium), and fomentation and washing with different extracts have also been prescribed frequently [1].

QUICK RESPONSE CODE

DOI:
10.13040/IJPSR.0975-8232.5(12).5088-96

Article can be accessed online on:
www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.5(12).5088-96

A number of *arkas* (aqueous distillates) like, *ark Palash* (*Butea monosperma*), *ark Punarnava* (*Boerhavia diffusa*), *ark Mulethi* (*Glycyrrhiza glabra)*, in spite of being highly advocated preparations for various eye disorders in treaties like *Sushrut Samhita* (500 BC), they are seldom used by Ayurvedic physicians[1]. In the Ayurvedic system of medicine, as mentioned in ancient Indian books like *Charak Samhita*,*Sushrut Samhita*, *Rastarang* and *Astanghriday*, there are a number of plants which are used in ophthalmic disorders, either single or in compound formulations [2].

Ancient Investigations and Findings:

In *Sushrut Samhita* (500 BC), descriptions of various eye diseases and their etiology and treatment have been given in detail. Some of the diseases described and their modern counter parts are as under.

Sanskrit name of disease	
Abhishy and Adhimandh	Glaucoma

Timir Cataract
Adhyaman Tension
Grahshosh Orbital cellulitis
Netrashosh Atrophy or sinking of eye balls

Equivalent modern terminology Conjunctivitis

In *Shusrut Samhita*, besides surgery, treatments of above disorders have been also described, and some of them are as under [1]:

Disease recognized:

***Abhishyand* (Conjunctivitis):** The word *Abhishy and* derived from two word "Abhi" and "Shyandana" means discharge or secretion combined meaning is profuse discharge from all parts of eye. The disease *Abhishyand* is a Sarvagata Netra Roga which means it affects all parts of eye[3]. The gravity of Abhishyanda is that it often said to be cause of all type of eye disorders. *Adhimandh* (Glaucoma) *Timir* (Cataract) may directly cause if it not treated properly. Acharya Sushruta has enumerated it under communicable disease[3]. Rag and Lohit Netra (conjunctival congestion), sangharsh (foreign body sensation), Nistoda (pricking sensation), Daha (burning sensation) and paka (severe inflammation) often accompanied with mucopurulent discharge are the important signs and symptoms of *Abhishyanda* (Conjunctivitis) [3].

***Adhimandh* (Glaucoma):** The word *Adhimandh* derived from two words "Adhi" and "mandha" means loss of vision in other words called blindness. Glaucoma comprises a group of chronic conditions that is characterized by progressive deformation of the optic nerve head and elevated intraocular pressure (IOP), a risk factor. It affects primarily the middle aged and elderly, the glaucoma currently constitute second most common 2, 3 cause of treatable blindness worldwide [4].

- ***Timir* (Cataract):** In Ayurvedic terminology, cataract is termed *Linga Nasha* or *Timira*. According to Ayurvedic principles, such a condition develops due to the aggravation of Vayu. Vayu dries up things. Here, aggravation of Vayu dries up the liquid that makes the lens and the retina supple [4].

In general Cataract is the opacification (light impenetrability) of the lens. In this condition, the lens of the eyes interferes with the eye vision[5].

PREPARATION AND METHOD OF USE: AYURVEDIC OCULAR THERAPIES

When we refer Ayurvedic classics for therapeutic measures adopted for the treatment of eye diseases, many topical treatments along with some systemic ones are observable [6].The reason for preferring topical therapies might be non-crossing of the Blood aqueous, Blood vitreous, blood retinal barriers of the drugs administered systemically. The topical measures play a pivotal role and are called as 'Kriya Kalpas [6].

ROLE OF TOPICAL THERAPIES

The term Kriya Kalpa is composed of two words Kriya and Kalpa.
Kriya means the therapeutic procedures which cures the disease without causing any adverse effects.
Kalpa indicates the specific formulation adapted for the therapeutic procedures.
These are specifically designed according to the stage and severity of the disease.
Sushruta the father of Indian Ophthalmology mentioned six Kriya Kalpas.- Tarpana, Putapaka, Seka, Aschotana, Anjana, Arka
The two inclusions made by *Sharangadhara* and *Vagbhata* are -Pindi, Bidalaka[1, 6].

Therapies for eye disorders:

Fomentation: - *Seka*
Fomentation with decoction of *Kanthakari* (*Solanum xanthocarpum*) root, prepared with milk.
Fomentation with concentrated extract of either *Nagarmotha* (*Cyperus scariosus*) or *Sendha Namak* (*Rock Salt)* or *Mulethi* (*Glycyrrhiza glabra*) or *Pippali* (*Piper longum*) prepared with milk[1, 7].

Anjan:-
Paste of *Mulethi* (*Glycyrrhiza glabra), Harida* (*Curcuma longa*) *Harad* (*Terminalia chebula*) *Devdaru* (*Cedrus deodara*), in equal parts prepared with goat milk or water and concentrated. An Anjan (Collerium) is prepared and applied[1, 7, 8].

Arka: - Steam distillates of plants like *Punarnava* (*Boerhavia diffusa*), *Palash* (*Butea monosperma*),

and *Mulethi* (*Glycyrrhiza glabra*), used as eye drops[1, 7, 8].

Paste: -
Fine paste of drugs used as ointment [7, 8].

Washing:-
Washing of eyes with extract of drugs like Triphala comprising of three drugs viz. *Amla* (*Embica officinalis), Harad (Terminalia chebula) and Bahera (Terminalia belerica)* [1,6,7,8].

TABLE 1: MAJOR HERBAL DRUGSCOMMONLY USED IN EYE DISORDERS [1, 10, 11, 12]:

S.No.	Common Name	Botanical name
1	Amla	(*Embica officinalis*)
2	Harad	*(Terminalia chebula)*
3	Nagarmotha	(*Cyperus scariosus*)
4	Pippali	(*Piper longum*)
5	Mulethi	(*Glycyrrhiza glabra*)
6	Lodra	(*Symplecos racemosa*)
7	Kamal	*(Nelumbo nucifera)*
8	Vacha	*(Acorus calamus)*
9	Amaltash	*(Cassia fistula)*
10	Padam	*(Prunus ceraceoides)*
11	Lal chandan	*(Pterocarpus santalinus)*
12	Anant mool	*(Hemidesmus indicus)*
13	Daru haldi	*(Berberis asiatica)*
14	Punarnava	(*Boerhavia diffusa*)
15	Palash	(*Butea monosperma*)
16	Triphala	*(Emblica Officinalis, Terminalia belirica, Terminalia Chebula)*

Problems of Ancient Ayurvedic Formulations:
A preliminary study conducted on Ayurvedic formulations revealed that their pH is not at par with that of lachrymal fluid of eyes, resulting in high irritation.A major problem in ocular therapeutics is the attainment of an optimal drug concentration at the site of action. Poor bioavailability of drugs from ocular dosage forms is mainly due to the precorneal loss factors which include tear dynamics, non-productive absorption, transient residence time in the cul-de-sac, and the relative impermeability of the corneal epithelial membrane. Due to these physiological and anatomical constraints only a small fraction of the drug, effectively 1% or even less of the instilled dose is ocularly absorbed[13]. The effective dose of medication administered ophthalmically may be altered by varying the strength, volume, or frequency of administration of the medication or the retention time of medication in contact with the surface of the eye [13].

This review is an attempt to focus on the recent findings, development in the ocular drug delivery system. Various approaches being used to improve the corneal penetration of a formulation and delay its elimination from the eye are discussed in details in the Modern counterpart of present review[13, 14].

MODERN INVESTIGATIONS AND FINDINGS:
The use of medicinal plants is based on the experience of many generations of physicians and traditional systems of medicine from different ethnic societies [15]. The use of medicinal plants in modern medicine suffers from the fact that although hundreds of plants are used in the world to prevent or to cure diseases, scientific evidence in terms of modern medicine is lacking in most cases. However, today it is necessary to provide scientific proof as to whether or not it is justified to use a plant or its active principles [15]. Ophthalmic disease problems afflict a substantial portion of the population [15].The descriptions of disease following approaches are expected to increase the modern application of traditional knowledge for their scientific rationality and therapeutic application[16].

Disease recognized: In modern era the following disease have been recognized[17].

Presbyopia. This is the loss of the ability to clearly see close objects or small print. It is a normal process that happens slowly over a lifetime, but you may not notice any change until after age 40. Presbyopia is often corrected with reading glasses.

Floaters. These are tiny spots or specks that float across the field of vision. Most people notice them in well-lit rooms or outdoors on a bright day. Floaters often are normal, but can sometimes indicate a more serious eye problem, such as retinal detachment, especially if they are accompanied by light flashes.

Dry eyes. This happens when tear glands cannot make enough tears or produce poor quality tears. Dry eyes can be uncomfortable, causing itching, burning, or rarely some loss of vision.

Tearing. Having too many tears can come from being sensitive to light, wind, or temperature changes. Tearing may also mean that have a more serious problem, such as an eye infection or a blocked tear duct.

Cataracts. Cataracts are cloudy areas that develop within the eye lens. Since the lens in a healthy eye is clear like a camera lens, light has no problem passing through the lens to the back of the eye to the retina where images are processed. When a cataract is present, the light cannot get through the lens as easily and, as a result, vision can be impaired. Cataracts often form slowly, causing no pain, redness, or tearing in the eye.

Glaucoma. This condition occurs when there is a typical and progressive deterioration of the optic nerve. Glaucoma is often associated with an increased pressure of the eye. The eye is like a tire that generally has a normal and safe pressure. When this pressure is increased, it can be associated with damage to the optic nerve; this is called primary open angle glaucoma.

Conjunctivitis. This is a condition in which the tissue that lines the eyelids and covers the cornea becomes inflamed. It is sometimes called "pink eye" or "red eye." It can cause redness, itching, burning, tearing, discharge, or a feeling of something in the eye. Conjunctivitis occurs in people of all ages and can be caused by infection, exposure to chemicals and irritants, or allergies.

Corneal diseases. The cornea is the clear, dome-shaped "window" at the front of the eye. It helps to focus light that enters the eye. Disease, infection, injury, and exposure to toxic agents can damage the cornea causing eye redness, watery eyes, pain, reduced vision, or a halo effect. Treatments include making adjustments to the eyeglass prescription, using medicated eye drops, or having surgery.

Eyelid problems. The eyelids protect the eye, distribute tears, and limit the amount of light entering the eye. Pain, itching, tearing, and sensitivity to light are common symptoms of eyelid problems. Other problems may include drooping eyelids, blinking spasms, or inflamed outer edges of the eyelids near the eyelashes. Eyelid problems often can be treated with proper cleaning, medication, or surgery.

Temporal arteritis. Also known as giant cell arteritis, this condition is an inflammation of the arteries throughout the body. It can begin with a severe headache, pain when chewing, and tenderness or swelling in the temple area. It may be followed in a few days or weeks by sudden vision loss - usually in one eye. Other symptoms can include shaking, weight loss, and low-grade fever. Scientists don't know the cause of temporal arteritis but they think it may be caused by an impaired immune system. Sudden vision loss in the other eye may occur within a few days or weeks of the first eye.

Recent Advances in Ayurvedic Ophthalmic Drug Delivery System [13, 18, 19].

Viscosity modifiers: Polymer forms a back bone of a dosage form developed to prolong the precorneal residence time of topically applied drugs. First attempt made to prolong the contact time of applied drug with cornea was to increase the viscosity of the preparation. The viscosity modifiers used were hydrophilic polymers such as cellulose, polyvinyl alcohol and poly acrylic acid. Polysaccharides such as xanthan gum were found to increase the viscosity and delay the clearance of the instilled solution by tear flow. Herbal drugs of various solubility incorporated into these polymers to form gels.

These polymers have high molecular weight which cannot cross the biological membrane, *Patton and Robinson* reported that increase in corneal penetration of ophthalmic drug would be maximum at viscosity of about 15 to 150 cp., further increase in viscosity associated with blurring of vision and resistance to eyelid movements. *Greaves et al*., reported that formulation of polymers that display non newtonian properties offer significantly less resistance to the eyelid movements. Viscosity of vehicles increases contact time but there is no marked sustaining effect.

Mucoadhesive polymers:

Goblet cells in the cornea secrets glycoprotein which forms a thin film over cornea called as mucin. Mucin is capable of pinking about 40-80 times its weight in water as it consist of very large

linear peptide chain to which large no of oligosaccharides chains are bound. Attractive drug delivery is application of natural and synthetic polymers that will attach to mucin and will remain in vicinity of mucin as long as it is present and these polymers are referred as mucoadhesive polymers. Large range of polymers is available and various researchers have given methods to characterize the bio adhesion of such polymers [20, 27]. *Robinson* reported that polyanions are better in bio adhesiveness and toxicity as compare to polycations [19].

Following mucoadhesive polymers are used most of the times in various ophthalmic drug delivery systems.

Polyacrylic Acid:

Corbopol:

Cross linked polyacrylic acid to have excellent mucoadhesive properties causing significant enhancement in ocular bioavailability[8]. Carbopol934 P is high cross link water swell able acrylic polymer with molecular weight approximately 3000000 Da. which is appropriate to use in pharmaceutical industry. *Park Robinson and Ponchel et al*. reported that poly acrylic acid interact with functional group of mucus glycol pro tien via carboxylic group. Precorneal residence of carbopol solution found to be greater than that of PVA solution when devis et al. evaluated corneal clearance of pilocarpine in carbopol 934P solution compare to that of end equiviscous non mucoadhesive PVA solution and buffer (PBS) in the rabbits [28,29].

Saettone et al. carried out much experiment with pilocarpine, the poly acrylic acid (5%w/v) carbopol 941P form a stable precorneal film and with less solubility[30,31]. Drug duration of stable film effect significantly increases as compare to pilocarpine[30, 31]. Weinreh et al. found that suspension beta hexabol base on the poly acrylic acid provided a more constant release of betaxol that its solution[32]. Thermos et al. evaluated ocular bioavailibity of timolol in isoviscous solution of PVA (PAA and timolol PAA salt). The result suggested that PAA polymer produce lower ocular concentration that those after PVA and slower the release of timolol and resulting in longer retention of vehicle in cunjuctivital sac by mucoadhesion [33].

Use of carbopol in ophthalmic drug delivery having following advantages and disadvantages: Gel prepared for ophthalmic administration using carbopol are more comfortable than solution, or soluble inserts though they are instilled like ointment less blurring of vision occurred as compare to ointment. However, disadvantages are no rate control on drug instability and it leads to matted lids[34].

Polycarbophil:

It is cross linked poly acrylic acid polymer which is insoluble in water but swells and can incorporate large quantity of water. Carbophil cross linked with divinyl glycol found to give good bio adhesion as compare to conventional non bio adhesivesuspension[35.]

Carboxymethyl cellulose:

Sodium CMC found to be excellent mucoadhesive polymer. Ophthalmic gel formulated using NaCMC, PVP and corbopol on the in vivo studies on the gel showed diffusion coefficient in corbopol 940 1%> NaCMC 3%> PVP 23%. Recent research suggests that adhesive strength increases as molecular weight increases up to 100000 da[36.]

***In -situ* gelling systems:**

In early eighty's concept of in situ gelling come existence these systems will have low viscosity and will be instilled as eye drops and will change in to gel like system when in contact with corneal fluid. This sol to gel transition can be brought about by three ways. Change in temperature, change in pH and ion activation[37].

pH triggered system:

Cellulose acetate hydrogen phthalate latex, typically shows very low viscosity up to pH 5, and forms clear gel in few seconds when in contact with tear fluid pH 7.2 to 7.4 and hence, release contents over prolong period of time. Use of such pH sensitive latex described by Gurny et al. the half-life of residence of CAP dispersion on corneal surface was approximately 400 seconds as compare to 40 second for solution[38]. However, this system is

associated to discomfort to patient due to high polymer conc and low pH of instilled solution[39].

Change in temperature:

Poloxamer F127 is in the form of solution in room temp and when this solution is instilled in to eye phase transition occurs from solution to gel at temp of eye thereby prolonging its contact with ocular surface. Pluronic polyol represent a class of block copolymer consisting of (polyoxyehylene and polyoxypropylene units). No of these units and their ration per mol of polymer provide wide range of polyol with different physical and chemical properties[40].

Ion activation:

Gelrite is a polysaccharides, a low acetyl gellan gum shows phase transition in presence of mono or divalent cations. Timolol bioavailability found to be superior with geltrite over equiviscous HEC solution[41].

Colloidal systems:

Main object in optimization of ocular drug delivery is to increase the contact time of drug with conjunctiva[42]. Colloidal carriers like liposomes nano particles found to be useful to prolong the corneal contact time and hence more and more tested in ocular drug delivery. Smolin et al.[43] for the first time studied application of liposome for ocular drug delivery. Liposomal suspension of idoxuridine found more efficient in the presence of herpex simplex keratitis in rabbit as compare to idoxuridine solution[44]. Similarly significant increase of triamicinolone in aqueous humor found from the administration of encapsulated trimcinolone in liposomes[45]. However, result after administration of pilocarpine 0.1 % in liposomes in terms of intraocular pressure found disappointing when compared with pilocarpine isotonic buffer solution[46]. Same result obtained with dihydrosteptomycin sulphate after administration in the form of liposomes[47].

From above result it is concluded that encapsulated drugs physico chemical properties have significant influence on the effect of liposomes[48]. Favorable result with liposomes found essentially with lipophilic drugs. Reason for this suggested being that hydrophilic drug escape rapidly out of the liposomes than lipophilic drugs[49]. Charge on liposomes also influence drug concentration in ocular tissues[50]. Corneal epithelium is covered by negatively charged mucin and all authors agreed that positively charged liposomes increase drug concentration in ocular tissues[51].

Nanoparticles are polymeric colloidal particles ranging in size from 10-100nm. Various polymers like polyacrylamide, polymethyl methaacrylate, albumin gelatin, polyalkylcynoacrylate, polylactic-co-glycolic acid, ε-caprolactone used in the preparation of nanoparticles[52]. First study using nanosphere done on system constituted of pilocrpine-loaded Nano sphere of polymethyl methacrylate acrylic acid copolymer by Gurny et al. developed pH sensitive latex nanoparticles for pilocarpine and result found to be promising[53]. In another study binding of pilocarpine to polybutyl cynoacrylate nanoparticles enhanced the mitotic response by about 22 to 33 %[54].

Ophthalmic insert:

Ophthalmic insert defined as sterile preparation with solid or semisolid consisting and whose size and sharp are especially designed for ophthalmic application[56]. They offer several advantages as increase ocular residence, possibility of releasing drug at a slow constant rate, accurate dosing and increased shelf life with respect to aqueous solutions. Two types of Ocuserts® are available in the market[57]. Various polymers tried in ophthalmic inserts were polyacrylic acid, polyvinyl alcohol, silicone elastomer, hydroxy propyl cellulose, ethyl cellulose cellulose acetate phthalate and polymethacrylic acid, hyaluronic acid. Possibility using biopolymers such as fibrin chitosan for preparation of soluble or erodible insert has been also reported in literature[58].

Ocular Iontophorosis:

Ocular iontophorosis offers drug delivery system that is fast pain less safe and result in delivery of high conc of drug to specific site[59]. Studies on ocular iontophorosis of 6-hydroxydopamine and methyl para tyrosine carried by number of investigators. Iontophoresis application of antibiotics may enhance bactericidal activity of the antibiotics and reduce the severity of the disease[59-62].

TABLE: 2 LIST OF SOME MODERN AYURVEDIC FORMULATIONS IN VARIOUS TYPES OF OCULAR DISEASES

S.no.	Scientific name	Common name	Family	Uses in ocular disease	Dosage form	References
1.	*Boerhavia Diffusa*	Punarnava	(Nyctaginaceae)	night blindness and conjunctivitis	Aqueous distillate	Thirumurthy*et al* [16]
2.	*Sesbania grandiflora*	Hadaga, Agati	Fabaceae	Conjunctivitis	*in situ* gel	Wagh *et al* [63]
3	*Terminalia chebula*, *Terminalia bellirica*, and *Phyllanthus emblica*,	Triphala		Antimicrobial Antioxidant.	Eye drop	Sawant*et al* [66]
4	*Nigella sativa*	Kalonji	Ranunculaceae	Catarct	Ethanolic extract	Ahmed*et al* [65]
5.	*Emblica officinalis*	Amla	Euphorbiaceae	Catarct	Eye drop	Meena*et al* [5]
6.	*Ocimum sanctum*	Tulsi		Catarct	Aqueous distillate	Meena*et al* [5]
7.	*Trigonella foenum*	*graecum*	Fenugreek	Cataract	Eye drop	Meena*et al* [5]
8.	*Cheilanthes glauca*	(Cav.)	Adiantaceae	Cataract	Eye drop	Meena*et al* [5]
9.	*Terminalia chebula*, *Terminalia bellirica*, and *Phyllanthus emblica*,	Triphala	CombretaceaeCombretaceaeEuphorbiaceae	Computer vision syndrome	Tarpan	Sawant*et al* [66]
10	*Honey and Rose water*	-	-	Cunjuntivitis	Eye drop	Bhardwaj*et al* [3]
11.	Butea Monosperma	Palash	Fabaceae	Cataract	Eye drop	Srikanth*et al* [67]

CONCLUSION: Ayurveda is one of such inherited tradition of health and longevity. A wide variety of plants have been found to have effective against number of ocular diseases. In this review the information is recorded, the plants used in treatment of ocular diseases. This review helps the researcher to develop new formulations for eye disorders, which will beneficial for the society in future era.

Future scope:

The review of wide body of research papers, review articles and ancient Ayurvedic books, represented as above, could be concluded as; Considerable research work already done proves that the herbs really has benefits to eyes

(Chaksushya). In terms of individual eye diseases further research needs to be undertaken to establish the authentic activities in eye. Confirmation of these activities will be assured by pharmacological activity on experimental animals.

ACKNOWLEDGEMENTS: My sincere thanks to Dr. Anurag Verma, Director, School of Pharmaceutical Sciences And Research, IFTM University, Moradabad U.P. and Dr. V.K. Lal Director Sagar Herbal Research Centre, Barabanki, U.P., for their support and kind guidance in review writing and providing necessary facilities.

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How to cite this article:
Pooja, Lal VK and Verma A: A Review on Ayurvedic Medicinal Plants for Eye Disorders from Ancient to Modern Era. Int J Pharm Sci Res 2014; 5(12): 5088-96.doi: 10.13040/IJPSR.0975-8232.5 (12).5088-96