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Smart polymeric eye gear: A possible preventive measure against ocular transmission of COVID-19

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ABSTRACT

The angiotensin-converting enzyme 2(ACE-2) receptors with approx. 0.8% congestion in conjunctival surface, leads to increase susceptibility of Covid-19 transmission through ocular surface. It has been observed that prophylactic measures such as goggle or face shield are unable to offer complete protection against ocular transmission of SRS-CoV-2. Hence, it is hypothesized that topical ocular prophylaxis using biocompatible polymers with reported *in-vitro* and *in-vivo* evidence of ACE inhibition and antiviral activity appears to be a promising strategy for preventing ocular transmission of Covid-19 to healthcare workers. They are capable of binding to ACE-2 receptors which may provide highly potential trails to block virus entry to host cells. Further biopolymers imparting antiviral activities greatly improve their protective performance. They not only provide prolong protection but also are safe for long-term use. This article discusses the description of structural and functional attributes of ACE-2 to identify appropriate polymer with better binding affinity. Furthermore, potential polymers with appropriate concentration are suggested for evaluation through a hypothesis to consider them for Covid-19 implication.

Introduction

The global scenario of Coronavirus diseases-2019 (Covid-19) is drastically changing. Researchers across the world are struggling to cope with the COVID-19 menace with almost 5 lakhs death out of a total number of cases crossing 1 crore mark [1]. As more evidence is getting accumulated for the possible ways of infection, all the possible avenues must be examined properly to reduce the risk of infection. Coronavirus 2 (SARS-CoV-2) is thought to have both respiratory and extra-respiratory routes of infection. ACE-2 receptor is appeared to be the cellular doorway for the SARS-CoV-2. The eye is reported to have ACE-2 receptors both on conjunctiva and retina. There are clinical manifestations such as pink eye, chemosis and epiphora observed in Covid-19 patients, support the concern of ocular transmission. Hence the theory of ocular transmission cannot be rejected completely with the COVID-19 scenario [5,6]. Previous reports with influenza, suggests that the ocular route can be a potential route for virus transmission [4]. An effective barrier protecting the eye is of paramount importance because the droplets and body fluids have a high probability to get onto the conjunctiva surface [12,13]. Hence safety goggles and single or multidose antihistamine/antiviral/antibiotic or steroidal eye drops are alternative pre and post-treatment measures identified to reduce ocular transmission [7–9]. However, they do not have the complete ambit of controlling the infection mechanically as well as therapeutically. Also, the regular use of antimicrobial eye preparation as a prophylactic measure can lead to permanent loss of vision. Bhattacharyya et al. in their study stressed povidone-iodine (1%) for post-exposure prophylaxis with toxicity study [10]. Antiviral drugs or small molecular inhibitors targeting specifically for SARS-CoV infection are in the phase of the invention. Fusion inhibitors such as Transmembrane protease, serine 2(TMPRSS2), and moieties blocking the interaction of spike protein (SP) with ACE-2 furin site are few areas that need to be explored for preventing ocular transmission [11]. These studies might recruit many candidates and hopefully in the long battle and few hits would emerge successfully. As the cases are rising, the trend of ocular infection in the future can be expected to get addressed soon.

There are reports of inflammation in both anterior and posterior segments of the eye during infection. So, ACE-2 receptors blocking beforehand can be a partial or a complete prophylactic success. The receptor-binding domain of the spike protein in the SARS coronavirus is not affected by the single point mutation [14,15]. The carbonyl group and the amide group of amino acids are docked through hydrogen

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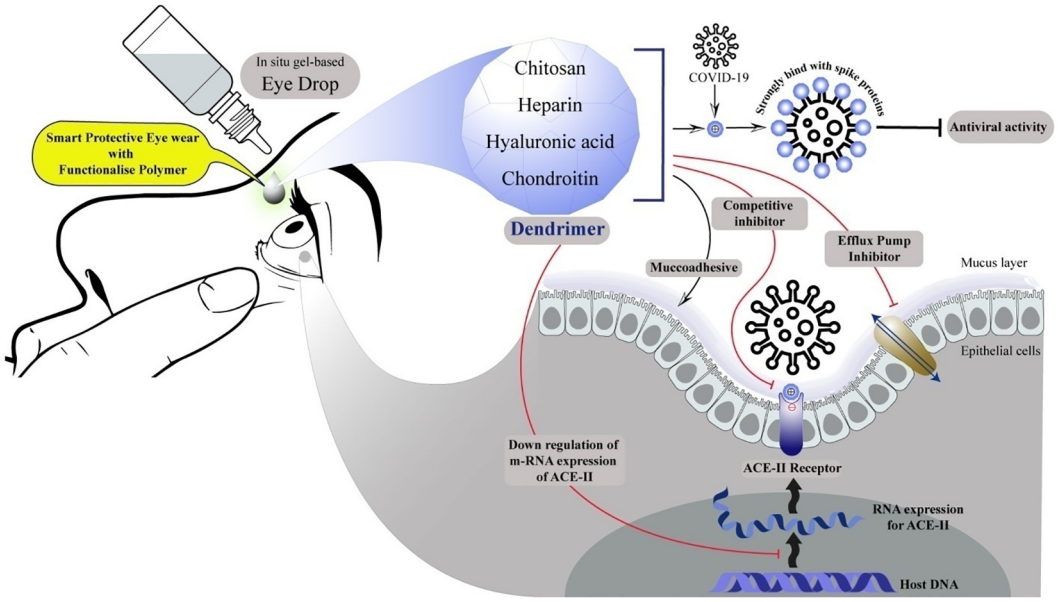

Fig. 1. Represents multifunctional aspects of mucoadhesive polymers preventing ocular transmission of COVID-19.

bonds at various locations during the interaction. Hence the binding efficiency with the ACE-2 receptor is not altered to a great extent [16,17]. However, keeping in mind the small residual amino acid exposure, low molecular weight, and short-chain ligands could be the key to thwart the interactions. However, it needs extensive pre-clinical and clinical investigation to ensure a safe and long-run success as a protective eye gear.

Looking at the rate of transmission of Covid-19, there is an immediate need for a safe and effective protective eye gear. Polymer-based eye drops are the modern-day treatments for chronic ailments of the eye. To the best of our knowledge, no studies have been conducted on natural polymers against the Covid-19 virus in ocular infections. Previous studies indicate natural polysaccharides with their derivatives such as hydroxypropyl guar, sodium hyaluronate, chondroitin sulfate, dextran, have shown antiviral properties in *in-vitro* experiments. In addition to the protection of viral entry-level, underlying antiviral activities of the above polymers offer additional protection against virus transmission. Most importantly, they are non-toxic, nonimmunogenic, biocompatible, biodegradable and do not influence the tear turnover rate. They can prevent oxidative stress and inflammation of the eye too. Fig. 1 depicts the different mechanisms of proposed polymers, helps in preventing ocular transmission of Covid-19.

Further, a regime of smart multifunctional bio-responsive polymeric materials sensitive to biochemical signals or pathophysiological conditions is considered as promising therapeutic platforms for the formation of next-generation medications. Armed with a proper understanding of different biologically responsive processes, scientists have made a significant contribution in the areas of polymer science to develop stimuli-responsive materials for a wide range of applications including bio-responsive targeted drug delivery, diagnostic and biomedical application. These polymers because of their unique ability of reversible phase transitions in response to a mild change in internal or external stimuli are also called a smart polymer. The individual polymer can undergo conformational changes at the receptor surface through dynamic molecular adjustments to facilitate the formation of shielding domains for viruses. Moreover, natural intelligible polymers studied for ocular adversaries seem to have no potential interaction with the host lipid cell membrane, ocular transmittance, oxygen permeability hence considered optimal for the ocular application. The functionalization of these polymers improves biocompatibility, mucoadhesiveness, drug encapsulation efficiency, antimicrobial activity, drug delivery performance, mucoadhesive properties, etc. The specificity of the polymers could be programmed to gear them up for a variety of challenges either triggered at the cellular or through incoming environmental pathogens. The following sections discuss the distinct biological properties of selected polymers to illustrate their possible application to prevent ocular transmission of Covid-19. Simultaneously, a hypothesis can be tested for various mucoadhesive polymer's potential to prevent the ocular route of infection.

Hypothesis

It is established that ACE-2 expression levels determine the extent of risk to the different organs of the human body. The ophthalmic route of infection has been under debate because clinically positive cases turned out to be negative with the tears or conjunctiva scrap samples in initial days of infection. But shreds of evidence are indicating a small percentage of cases tested positive with conjunctiva swab [2,3]. Our hypothesis further supported by literature evidence from Milewska and his team, where authors claim cationic chitosan and its hydrophobic derivatives exhibit strong interaction with the S protein of HCoV-NL63 and subsequently blocks its interaction with ACE-2 [23]. As mentioned earlier coronavirus uses its spike protein to enter into host cells via ACE-2 entry receptor. Recent literature based on the docking study revealed that the S1 protein of Covid-19 utilizes one of the highly negative domains of ACE-2, that enable viruses to enter into the host cell [17]. The above findings strongly favor the use of polycationic polymers and their derivatives in the protection of viruses at the entry site. Literature findings further suggest the protective role of heparin against SARS-CoV-2, which is attributed to the binding affinity of heparin sulfate for Spike S1 protein of Covid-19 [18]. Thiolated forms of the polymers have a high affinity for the ACE-2 receptor because of –HS group interaction forming disulfide bonds. They can give suitable mechanical integrity and more spatial orientations for bonding. Thiolated poly(acrylic acid), thiolated chitosan, thiolated hyaluronic acid, thiolated quaternary ammonium-chitosan conjugates, thiolated poly(aspartic acid) can have grave implications for the ACE-2 temporary blocking with some gaps to restore the functionality of the receptor [18,19]. They do have an inhibiting effect on the efflux pumps too. Dendrimers with a size range of 1–100 nm have multiple functional groups. Lower generation dendrimers having anionic or neutral surface can interact with the corneal surface featuring no toxicity to the eye.

Polypropylene Imine dendrimer (PPI), Poly(amidoamine) dendrimers (PAMAM), Poly-l-lysine dendrimers cationic in nature can interact with the ACE-2 receptor to downregulate the mRNA expression, however, toxicity must be resolved to use them in research [20,21]. Chitosan, a natural polysaccharide at 0.1% is found to be antiviral for common cold adenovirus NIH-3 T3 infected mice [22]. *In-situ* gels based on chitosan have high retention time due to surface interaction of its amine with the mucinous layer on the eye surface. Other polymers such as chitosan n-acetyl cysteine conjugate for enhanced precorneal retention, tamarind seed polysaccharide (TSP), and hyaluronic acid (HA) used for the dry eye syndrome may be suitable for use in enhancing the receptor blocking effect. Besides, viricidal activity, marine polysaccharides are can improve the immune responses of the host. They have free carboxyl groups to interact with the mucin surface for mucoadhesive properties [23].

Evaluation of the hypothesis

It may be deduced from the above mechanistic observations narrated in the hypothesis that biopolymers are worth investigating for ocular Covid-19 infection. A retrospective study of the following polymers may unfold appropriate molecular weight and concentration to initiate the studies. As natural polymers for shielding the ACE-2 receptor, few materials are anticipated for the hypothesized future research works in Table 1.

Chitosan

Chitosan is a natural polycationic polymer comprising of glucosamine and N-acetyl glucosamine subunits. Chitosan has been extensively investigated as a potential biomaterial for several biomedical applications because of its controlled drug delivery, biocompatibility, stimulus-responsive phase transitions, antimicrobial activities and easy functionality. The degree of biological activity of Chitosan is mostly depending on the availability of free functional groups (–OH, $–NH_2$). Chemical reactions like deacetylation, depolymerization, or appropriate chemical modifications are commonly employed to introduce functional groups for improved therapeutic success and low toxicity. The higher degree of deacetylation ensures more corneal retention and no inflammation. Xing et al. prepared a modified chitosan polymer with an increasing number of amino groups and found enhanced antiviral activity against new castle virus [24]. Wu et al prepared a polyelectrolyte complex of chitosan with hyaluronan and got the composite stabilized with zinc. The antiviral activity of the developed complex was increased against HIV, which could be attributed to their ability to block the entry point of HIV to the host cell [25]. Li et al prepared an ionic complex of chitosan with sialyloligosaccharides (SOS) and tested against influenza (H1N1) and found that a higher ratio of SOS results in increased adhesion, more cytoprotective and a potential anti-influenza agent [26]. Further chitosan due to its distinct chemical properties exhibits pH-dependent sol-gel transition, typically turn into a low viscous gel at alkaline pH of the eye, ensures prolong corneal retention, efficient ocular drug delivery, long-lasting lubrication and greater surface wetting makes it a suitable polymer for ocular application [27].

Heparin

Heparin is a natural polysaccharide consisting of hexuronic acid and glucosamine. Heparin due to high glycosaminoglycan content is strongly hydrophilic and forms a viscous gel with excellent corneal lubrication. Apart from this, it supports corneal healing and regeneration of damaged cells. It has also other advantages such as it blocks the complement cascade reaction near the inflammatory zone in the eye. Essentially it has antiallergic and immunoregulatory properties which are vital for Covid-19 application [28,29]. Literature evidence suggested that viral envelope proteins bind to the negatively charged

Table 1
A list of possible polymers that could be useful for blocking the Covid-19 infection through the eye.

Polymer	Concentration for ocular delivery	Desired Molecular weight in kilodalton(kDa)	Antiviral/other ocular friendly properties	Ref.
Chitosan	0.1%	3–5 chain of oligosaccharide of MW 4.1–5.6 kDa	70% difference in transfection observed through fluorescence for GFP adenovirus	[22]
Tamarind seed polysaccharide	0.7–1.5%	~33 kDa	Reported for chikungunya virus infection	[37]
Sodium hyaluronate	~0.2%	~50 kDa	Inhibit the in-vitro replication of Herpes simplex virus (HSV), Respiratory syncytial virus, retroviruses, adenovirus	[18]
Sodium alginate	~1%	~50 kDa	Swelling characteristic with part of the various antiviral mixture	[38,39]
Heparin	< 100 IU/ml	< 10 dodecasaccaharide unit of 5.6–6.4 kDa	Prevents the electrostatic interaction of JEV, YFV, ZFV	[30]
Chondroitin sulfate	~0.1%	~50–100 kDa	Binds to Zika virus envelope	[40]
Dextran	> 0.1%	~4 kD	Low molecular weight 40kD inhibitory for HSV	[41]
Thiolated hyaluronic acid	~0.5%	~80 kDa	High biocompatibility with very less toxicity and act against HSV	[42]
Thiolated chitosan	0.5–1%	~40 kDa	A component for higher mucoadhesive strength, increasing permeability	[43]
Thiolatedpolyasparitic acid	3%–5%w/w	~5 kD	Do not induce lachrymation	[44]
Dendrimer	10 μM	–	G (1.5)-16COONa and G (5)-128SA cause 40% decrease in plaque formation against MERS-CoV	[21]

glycosaminoglycans (GAG), contribute to its overall activity. The level of antimicrobial activity influenced by varying lengths, sequence and degree of sulfation of heparin. Kim et al. studied low molecular weight heparin (LMWH), heparin dodecasaccharide (dp12HP) for in-vitro antiviral activity againstZika fever virus (ZFV) in Vero cells and found 40% reduction in viral binding [30].

Dextran

Dextran is a natural hydrophilic polysaccharide consisting of α-1,6 and 1,3 linked d-glucopyranose. Dextran has been established as a non-toxic, non-immunogenic, biocompatible and as potential plasma expander. Dextran exhibits good mucoadhesive properties and absorbs more amount of water that helps to relieve the corneal irritation through lubrication. The complex polysaccharide helps to maintain the structural integrity of the cornea accomplished through tissue culture experiments [31]. Dextran sulphate because of its high anionic features found to inhibit the fusion activity of several viruses. Kurskaya et al. prepared low molecular weight oxidized injectable dextran for the influenza A/H5N1 virus and they got antiviral properties both in-vitro and in-vivo conditions. Hence dextran could be further studied for stopping the transmission in Covid-19 [32].

Hyaluronic acid

Hyaluronic acid is a polyanionic non-sulfated glycosaminoglycan naturally found in the eye. Hyaluronic acid has proven tear film stabilizing, surface friction reducing properties. Hyaluronic acid because of its intrinsic anti-inflammatory properties, reduces the dose of non-steroidal inflammatory agents (NSAIDs). The small and medium-chain polymers have immunostimulatory activity. Being a dominant component of the extracellular matrix, it is safe for long-term use topically on the eye. The molecular weight of Hyaluronic acid seems to play an important role in regulating its biological functions. Cermelliand coworkers investigated the anti-viral potential of high molecular weight hyaluronic acid (1800 KD). The results show strong anti-viral activity against Coxsackievirus B5, while moderate activity against Herpes Simplex Virus-1 and Porcine Parvovirus and no activity against Adenovirus-5, Human Herpesvirus-6 and Respiratory Syndrome Virus [18]. The high amount of ionic charges at the surface believed to be interrupting the electrostatic interaction between the host cell and the virus. Further, it can be mixed with other viricidal polysaccharide polymer or appropriate surface modification helps to enhance antiviral potential [18,33].

Dendrimer

Dendrimers are synthetic polyvalent, three-dimensional branched structures with high ionic density at the surface. They are hydrophilic, biocompatible nano-range structure (1–100 nm) extensively studied for ocular applications to determine the therapeutic effectiveness of entrapped medicinal agents and proved effective. Short-chain polymers show high ocular permeability and hence found effective for posterior eye segment conditions. Lower generation dendrimers prevent viral interactions with healthy cells by blocking the receptor protein. Studies with HSV-I, HSV-II and HIV-I have shown their potential to block the entry at host cell hence they may serve as a promising candidate against the Covid-19 virus [34,35].

In-situ gel polymeric formulations

In-situ polymeric gel formulations are an accepted mode of the ocular delivery systems to extend their retention time. Prolong corneal retention helps to maximize its therapeutic effectiveness. The contributing factors such as pH, temperature and ions influence the sol-gel transition at the physiological conditions of the eye. Accordingly, polymers can be sensitized at the surface through the introduction of functional groups which can stabilize themselves in the biological environment. For example, thiolated chitosan as temperature-responsive polymer, polyacrylic acid as a pH-sensitive polymer and ionic polysaccharides sensitive to the ionic strength of the tear could be potentially be employed as antiviral in the future study. Further, modified polymers due to their high retention time compared to plain polymer allow improved interactions, thereby considered to be realistic forms of prophylaxis against ocular transmission of the virus [36].

Consequences of the hypothesis and discussion

Natural polymers are safe and have high translation value. Most of the natural polysaccharide shows potential antiviral activities in cell lines and pre-clinical studies. Further, the antiviral studies in humans can add attributes to the implications in the case of Covid-19 in limited time. The *in-situ* gel formulation can provide prolong retention time without interfering with the ACE2 receptor domain permanently. Moreover, the percentage of individual polymers can be modulated through a series of experiments desiring the antiviral properties without any ocular toxicity. If they were expected to be antiviral at particular concentrations, toxicity study may be undertaken further to corroborate the proposed mechanisms. In addition, a suitable ophthalmic preparation must be explored like nanoparticle laden in-situ gel to enhance the protective efficacy. The above attempts would decipher the reliability of natural polymers in prophylactic formulations as tools to cutting down pre- or post-exposure viral damage to the host conjunctiva and hence the transmission rate.

Funding and declaration of competing interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the hypothesis. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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