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REVIEW ARTICLE

Harnessing nanofibers for targeted delivery of phytoconstituents in age-related macular degeneration

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ABSTRACT

Age-related macular degeneration is a degenerative eye condition that affects the macula and results in central vision loss. Phytoconstituents show great promise in the treatment of AMD. AMD therapy can benefit from the advantages of phytoconstituents loaded nanofibers. There are opportunities to improve the effectiveness of phytoconstituents in the treatment of age-related macular degeneration (AMD) through the use of nanofiber-based delivery methods. These novel platforms encapsulate and distribute plant-derived bioactives by making use of the special qualities of nanofibers. These qualities include their high surface area-to-volume ratio, variable porosity, and biocompatibility. Exploring the use of nanofiber-based delivery methods to provide phytoconstituents in AMD treatment is a great choice for enhancing patient adherence, safety, and efficacy in managing this condition. This article explores the potential of nanofiber-based delivery methods to revolutionize AMD treatment, providing an innovative and effective approach to treat this condition.

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1. Introduction

Age-related macular degeneration is a condition that destroys the macula and impairs vision. Dry AMD and wet AMD are two distinct forms of Age-Related Macular Degeneration (AMD). Dry AMD is distinguished by the accumulation of drusen and accounts for 80 to 90% of AMD cases. Dry AMD progresses to wet AMD due to abnormal blood vessel growth beneath the retina. Even though wet AMD is much more severe, it only accounts for 10–15% of instances. AMD is a major public health concern since it is the third most common cause of blindness worldwide. Its prevalence varies with age impacting 10–20% of those over 60 years of age (Lim *et al*. 2012). The prevalence of AMD in those over 40 varies between 1.2% and 4.7%. Western India shows an average prevalence of 1.4% whereas southern India has the greatest prevalence at 3.1%. It is anticipated that the prevalence of AMD will increase dramatically as India's population ages. It is estimated that AMD therapy in India will have an annual economic impact of more than 1.5 billion USD (Gupta *et al*. 2007). By 2040, there will likely be 288 million AMD sufferers worldwide, up from an estimated 196 million in 2020 (Korva-Gurung *et al*. 2023). The primary cause of vision loss worldwide is age-related macular degeneration (AMD) however a permanent solution is still unattainable. It has a significant impact on center vision. Its effects are severe particularly in activities like driving and reading. Drusen, a common condition in aging eyes can lead to AMD and blindness. AMD develops in two stages: early/intermediate and advanced. This highlights how important it is to have efficient therapies in order to lessen the negative effects on individual's quality of life (Coleman *et al*. 2008).

Two major factors thought to be responsible for the development of AMD are oxidative stress and choroidal vascular dysfunction. Because of its abnormally high oxygen consumption, the retina is especially susceptible to oxidative stress which is a major factor in aging-related disorders like AMD (Thomas *et al*. 2021). The high oxygen demand of the retina, light exposure and the abundance of polyunsaturated fatty acids such as docosahexaenoic acid in photoreceptors cause oxidative stress in AMD. This causes an overabundance of reactive oxygen species which harms Bruch's membrane, photoreceptors, and the retinal pigment epithelium. Damaged RPE has trouble phagocytosing the outer segments of photoreceptors which leads to further ROS accumulation and structural failure. Malondialdehyde and carboxyethylpyrrole, the two indicators of oxidative stress build up and show both local and systemic harm. The course of AMD is accelerated by this cascade which compromises retinal integrity and causes lipid and protein deposits, cell loss and neovascularisation (Kushwah *et al*. 2023).

Oxidative damage in the retina leads to build up of cellular waste in the posterior segment of the eye. This activates immune mechanisms that include microglia and macrophages. Endothelial cells get activated and cause angiogenesis. Pro-inflammatory cytokines such as TNF-α, IL-6, and VEGF

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worsen inflammation. By producing angiogenic factors and breaking down the extracellular matrix, macrophages contribute to chronic inflammation (Heloterä and Kaarniranta 2022).

Reactive oxygen species (ROS) are produced by mitochondrial activity. On exposure to light, the retinal cells especially the retinal pigment epithelium (RPE) get seriously harmed. The accumulation of cellular waste results from the RPE's inability to process and eliminate it due to oxidative stress. Malondialdehyde and 4-hydroxynonenal, are the two byproducts of lipid peroxidation. They intensify inflammatory pathways including NF-κB signaling, which triggers the production of cytokines and sustains inflammation. The cellular damage leads to the development of drusen. The presence of drusen is a hallmark of dry AMD. Drusen deposits between Bruch's membrane and the RPE resulting to inflammation (Pinelli *et al*. 2020).

Drusen builds up between Bruch's membrane and the retinal pigment epithelium (RPE). This disturbs the photoreceptors' planar layout and results in mechanical derangement that causes visual symptoms including metamorphopsia and loss of contrast sensitivity. Drusen are linked to neoangiogenesis in wet AMD. The risk of progressing from dry to wet AMD increases with larger and more numerous drusen, as well as the presence of retinal pigment epithelium (RPE) pigmentary abnormalities (Abdelsalam *et al*. 1999). As drusen accumulate, they can lead to inflammation and the release of growth factors like vascular endothelial growth factor (VEGF). VEGF promotes the growth of new, abnormal blood vessels under the retina, a process known as choroidal neovascularization (CNV) which is characteristic of wet AMD. Wet AMD is considered an advanced stage of AMD. It can develop from any stage of dry AMD and causes sudden and significant vision loss (Figure 1).

The most significant symptoms of AMD are blurred vision, trouble perceiving in dim light, gradual loss of vision, low perception of depth, poor light/dark adaptation, distorted vision, difficulty perceiving contrasts, and loss of central visual field/central blind spot (Schultz *et al*. 2021). The main risk factors for AMD include age, health problems, genetics, and lifestyle choices. The risk of AMD rises with age, especially in people over 50. The development of AMD is closely linked to smoking, drinking alcohol, and consuming low amounts of antioxidants. AMD risk may also be increased by high-density lipoprotein cholesterol, genetics, and other medical disorders including hypertension (Wang *et al*. 2022).

1.1. Current treatment and their limitations

The focus of conventional AMD therapy is to stop the course of the disease and decrease vision loss. Although various treatments, like nutritional supplements and anti-VEGF injections can be useful, they have drawbacks and don't completely address the underlying reasons of AMD.

1.1.1. Current treatment for dry AMD

1.1.1.1. AREDS2 formula supplements. The AREDS2 formula is a specific combination of nutritional supplements designed to slow the progression of moderate to advanced age-related macular degeneration (AMD). It was developed based on the Age-Related Eye Disease Study 2 (AREDS2). The AREDS2 formula consists of Vitamin C (500 mg), Vitamin E (400 IU), Lutein (10 mg), Zeaxanthin (2 mg), Zinc (80 mg or 25 mg), and Copper (2 mg) to slow AMD progression while minimizing risks (Bernstein and Hobbs 2014). The AREDS2 formula slows AMD progression but also requires long-term adherence. It may cause gastrointestinal issues and high zinc levels can lead to toxicity in some individuals.

1.1.1.2. Pegcetacoplan and Avacincaptad Pegol intravitreal injections. Pegcetacoplan (Syfovre) and Avacincaptad Pegol (Izervay) are intravitreal complement inhibitors approved for treating geographic atrophy in advanced dry AMD. Pegcetacoplan helps reduce inflammation while Avacincaptad Pegol prevents retinal cell death (Girgis and Lee 2023). The limitations of this treatment includes the need for frequent intravitreal injections, high cost, risk of injection-related complications such as endophthalmitis and retinal detachment.

1.1.1.3. Photobiomodulation. Photobiomodulation is a type of light therapy for dry AMD. This treatment stimulates cellular activity and reduces oxidative stress in retinal cells by using visible to near-infrared (500–1000 nm) light from lasers or LEDs. It targets mitochondrial photoacceptors thus enhancing energy production, reducing inflammation and promoting cell survival (Merry *et al*. 2017). The limitations of photobiomodulation (PBM) for dry AMD include variable treatment outcomes, lack of long-term clinical evidence, uncertainty in optimal dosing parameters, need for repeated sessions and limited accessibility due to specialized equipment requirements (Laakso and Young 2013).

1.1.2. Current treatment for wet AMD

1.1.2.1. Anti-VEGF therapy. Anti-vascular endothelial growth factor (VEGF) medications such as Brolucizumab (a single-chain antibody fragment targeting VEGF-A), Aflibercept (a fusion protein that binds VEGF-A, VEGF-B, and placental growth factor) and Ranibizumab (a monoclonal antibody fragment targeting VEGF-A) are regularly injected via intravitreal injections. This medications attach themselves to VEGF molecules. They block their interaction with endothelial cell receptors and prevent angiogenesis and lessen retinal edema (Galindo-Camacho *et al*. 2022). Many people find anti-VEGF therapy to be effective but it has many drawbacks. Some patients exhibit continuous hemorrhage, growing lesions, fibrosis, and unresolved fluid exudation, among other signs of prolonged disease activity. Poor vision recovery is still a major worry highlighting the partial response to therapy in some situations (Mettu *et al*. 2021).

1.1.2.2. Photodynamic therapy. Verteporfin (marketed as Visudyne) is the only photosensitizer that is approved for the treatment of AMD. Photodynamic therapy (PDT) uses a special drug called a photosensitizer (PS). It gets injected into the vein and acquires in abnormal blood vessels under the macula. When a targeted laser light shines on these vessels, it triggers the drug leading to a chemical reaction that blocks the abnormal blood vessels and reduces their growth. The limitations of photodynamic therapy (PDT) for AMD include the possibility of recurrence of abnormal blood vessel growth, transient vision disturbances, and the requirement for repeated treatments over time (Beirão *et al*. 2025). Yoshida *et al.'s* study assessed the 3-year results of using aflibercept injections either standalone or

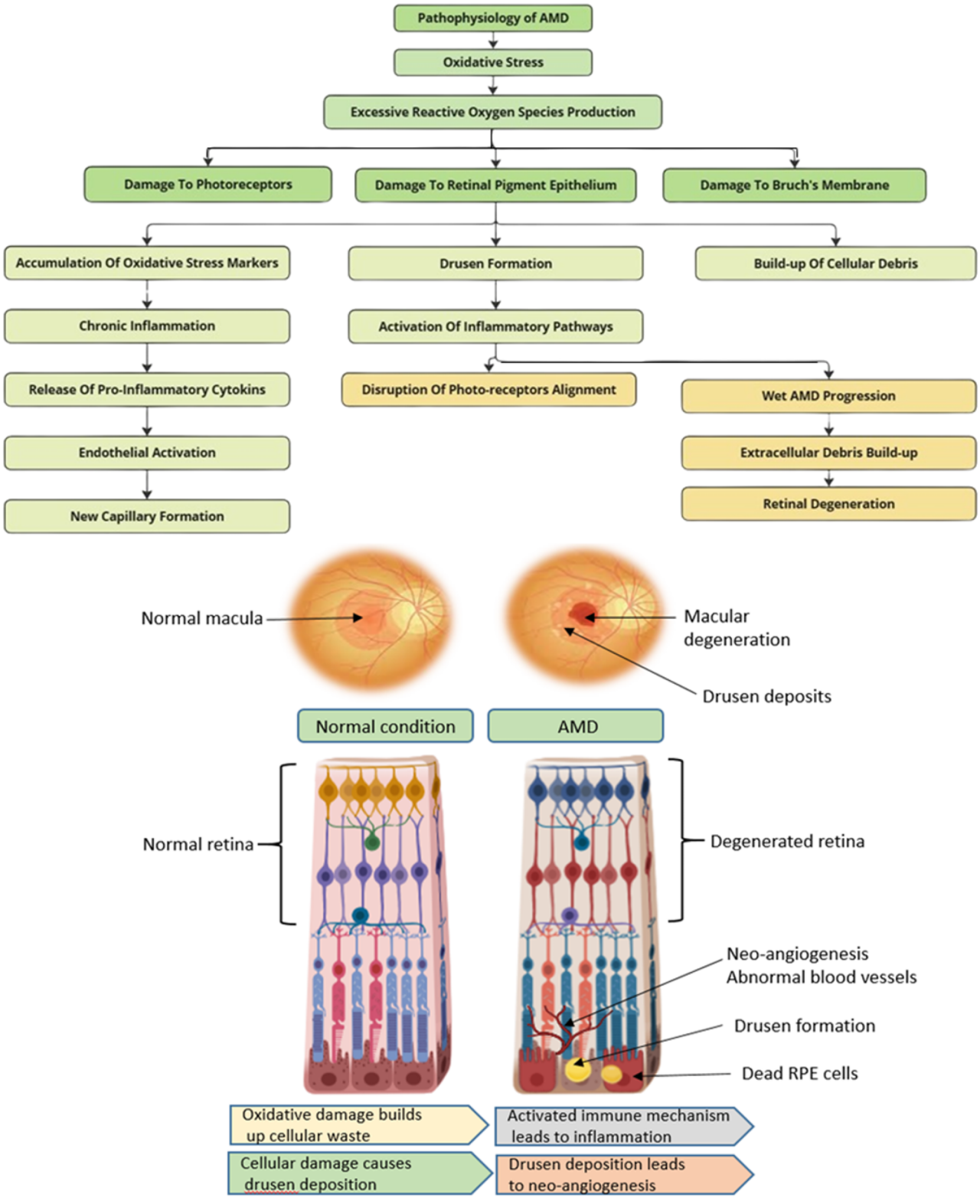

Figure 1. Pathophysiology of age-related macular degeneration. The role of oxidative stress, drusen formation, inflammation, and angiogenesis in pathophysiology of AMD (Deng et al. 2022, Kushwah et al. 2023) (created with Biorender.com).

in tandem with rescue photodynamic treatment (PDT) to treat neovascular AMD. Patients who got rescue PDT following the first year had a higher risk of developing macular atrophy. They suffered from worse visual outcomes even though visual acuity remained at baseline levels for 3 years. According to the research PDT may result in long-term issues such as macular atrophy even though treatment can be a lifesaver (Yoshida *et al.* 2022).

1.1.2.3. Laser therapy. Laser therapy to treat AMD uses concentrated light to cause controlled burns in the retina in order to promote retinal oxygenation and decrease aberrant blood vessel formation. Although this treatment aids in the disease's management, it may result in retinal damage and scarring, which could eventually cause vision loss (Chhablani *et al.* 2018). The potential of subthreshold nanosecond laser

(SNL) therapy to delay the progression of intermediate AMD (iAMD) to late AMD was investigated by Guymer *et al*. The findings demonstrated that in patients with reticular pseudodrusen, nanosecond laser did not stop the evolution of the disease and actually aggravated it. Laser therapy's primary drawback is that it may cause harm to some people (Guymer *et al*. 2019).

1.1.2.4. Nutritional supplements. Nutritional supplements such as omega-3 fatty acids, carotenoids (lutein and zeaxanthin), and antioxidants (vitamins C and E) may help reduce the onset of age-related macular degeneration (AMD). There are possible adverse effects at high doses, unknown ideal dosages and formulations, and uneven efficacy across studies (Mukhtar and Ambati 2019).

There are many drawbacks for existing therapies for age-related macular degeneration such as their limited efficacy in later stages, frequent injection requirements, and possible adverse effects. Advanced therapies have become more necessary to address these shortcomings. There is a need for less invasive, more focused, and longer-lasting treatments. This review deals with biocompatible nanofibers for the delivery of phytoconstituents in AMD.

2. Nanofibers as carrier

In pharmaceutical research, nanofiber-based drug delivery systems provide many benefits over conventional drug delivery techniques. Their high surface area-to-volume ratio enables effective loading and uniform dispersion of drugs. This property increases the drug-loading capacity of nanofibers by enabling them to encapsulate more drug within their polymeric structure. To maximize therapeutic efficacy, the vast surface area also allows precise control over the rate and duration of drug release (Gaydhane *et al*. 2023). The basic adaptability of distribution systems based on nanofibers is another benefit. During the production process, nanofibers' form, porosity, and surface chemistry can be adjusted. This allows formulation of delivery systems that are specifically designed to satisfy therapeutic requirements. Researchers can create drug delivery systems that target particular tissues or cells and have regulated release profiles. They can improve treatment outcomes while reducing adverse effects on healthy tissues (Singh *et al*. 2021). Another notable characteristic of nanofiber systems is their capacity to maintain medication release over extended periods of time. Nanofibers' distinct composition and structure allows for the continuous, regulated release of medicinal substances over long periods of time. By lowering the frequency of dose, this sustained release feature increases patient compliance and improves therapeutic efficacy by preserving steady medication levels at the intended location (Morie *et al*. 2016).

It is possible to deliver medications to diseased tissues by coating nanofibers with ligands. Site-specific delivery is possible for nanofibers by targeting ligands. These ligands bind to particular biological receptors or biomarkers. This reduces off-target effects (Goyal *et al*. 2016). This strategy is in line with the goals of precision medicine to provide personalized treatments that increase effectiveness and decrease side effects. Materials like biodegradable polymers which are biocompatible and biodegradable are used. Drug delivery systems based on nanofibers are safe for use in biomedical applications because of these features. Biodegradable nanofibers reduce tissue irritation and causes natural tissue healing. They slowly dissolve into nontoxic byproducts (Idrees *et al*. 2020). Drug delivery techniques based on nanofibers are highly biocompatible and biodegradable. Numerous therapeutic substances such as proteins, nucleic acids, tiny compounds, and even cells, can be delivered using these systems. As a result, systems based on nanofibers have great potential for use in drug delivery, tissue engineering, and regenerative medicine providing adaptable answers to a variety of medical problems (Goyal *et al*. 2016).

Nanofibers are becoming more acknowledged as an approach to ocular drug administration. This is due to their special structural characteristics and ability to prevent difficulties of delivering medicines to the eye caused because of conventional therapies. Nanofibers can pass through ocular barriers such as the corneal and conjunctival barriers as well as the blood-retinal barrier (BRB) because of their small diameter which is usually in the nanometer to micrometer range (Gaydhane *et al*. 2023). When it comes to traditional ocular drug delivery, these barriers prevent medications from getting to the intended site of action. Nanofibers can get past these physical obstacles and increase the bioavailability of therapeutic drugs in the eye because of their flexibility and nanoscale size. Delivery systems based on nanofibers can be customized for particular medications such as hydrophilic and hydrophobic substances as well as biologics like proteins or RNA. Nanofibers are appropriate for a wide variety of ocular conditions because of their adaptability (Uzel *et al*. 2023).

Sangole *et al*. formulated levofloxacin-loaded polymeric ocular inserts using polycaprolactone and hydroxypropyl cellulose for prolonged drug release in ocular infections while Altuntuğ Cesur *et al*. formulated latanoprost-loaded polyvinyl alcohol nanofibers crosslinked with 0.5% glutaraldehyde for the treatment of glaucoma. Both formulations were fabricated using electrospinning technique and produced uniform and bead-free nanofibers. In contrast, PCL/HPC inserts showed high drug-loading efficiency (101.70%), stable surface pH (6.81–6.83), and no drug-polymer interactions preserving drug integrity. Both formulations showed biocompatibility in vitro. Therefore electrospun nanofibers have the potential to improve therapeutic effects, decrease dosage frequency, and increase drug retention in ocular medication delivery (Sangole *et al*. 2022, Altuntuğ Cesur *et al*. 2024).

2.1. Fabrication methods of nanofibers

2.1.1. Electrospinning

Electrospinning is a crucial method in polymer science and nanotechnology. This method uses an electrically powered process to create ultra-fine fibers. The diameter ranges from nanometers to micrometers. In electrospinning, a polymer melt or solution is taken from a spinneret and subjected to an electric field. This creates a charged jet that lengthens and solidifies as the solvent evaporates. A high voltage between a

grounded collector and a metallic spinneret drives the process, overcoming surface tension to produce a Taylor cone from which a continuous jet emerges (Liao *et al*. 2008). By changing a number of parameters, such as solution concentration, viscosity, voltage, spinneret-collector distance, and ambient conditions, fiber final characteristics, like diameter and alignment, may be precisely adjusted. This degree of control makes it possible to customize the structure and shape of fibers. There are many electrospinning methods available, and each has special benefits for creating fibers with particular characteristics (Long *et al*. 2019, Wang *et al*. 2019).

Blend electrospinning creates composite fibers with specific mechanical, chemical, or physical properties by electrospinning polymer blends or several polymer solutions using a single spinneret. Multi-needle electrospinning, on the other hand, increases production efficiency and throughput by extruding polymer solutions using numerous needles (Alghoraibi and Alomari 2019). Majidnia *et al*. developed an ultrathin and porous fibrous film mimicking Bruch's membrane to serve as a carrier for retinal pigment epithelium (RPE) cells using blend electrospinning with a formic acid/acetic acid solvent. Higher HAMP content enhances scaffold hydrophilicity which is useful for cell adhesion and integration. Similarly Zhang *et al*. fabricated poly(L-lactic acid-co-ε-caprolactone) nanofibrous membranes combined with silk fibroin to develop a scaffold for in vitro retinal progenitor cell proliferation. Both studies show the potential of electrospun nanofibrous scaffolds for retinal tissue engineering by highlighting their biocompatibility and potential for cell attachment and growth (Zhang *et al*. 2015, Majidnia *et al*. 2022).

Emulsion electrospinning is a method that uses emulsions to create nanofibers. It is useful for encapsulating delicate bioactive substances. This technique helps to encapsulate both hydrophilic and hydrophobic drugs by reducing the active ingredients' direct exposure to organic solvents, which is particularly helpful when the active ingredients are sensitive to these solvents (Hu *et al*. 2015). Norouzi *et al*. worked on emulsion electrospinning to create core-shell ALG/PCL nanofibers. The process created a stable water-in-oil (w/o) emulsion. The sample extracts showed no hazardous effects according to in-vitro cytotoxicity tests. The findings indicated that the ALG/PCL core-shell nanofibers have good potential for biomedical uses (Norouzi *et al*. 2022).

Core-shell nanofibers are made via coaxial electrospinning. The shell shields the active bioactive element or medicinal ingredient from premature release while the core contains it. Two solutions are used. One acts as the core and one for the shell. Both solutions can be electrospun simultaneously using a double-compartment syringe with a concentric needle configuration. This method inhibits fast diffusion from the core and improves the stability and effectiveness of encapsulation while providing regulated and sustained drug release (Su *et al*. 2012, Pant *et al*. 2019).

2.1.2. Template synthesis

Template synthesis is a flexible and accurate method for creating nanofibers (NFs) with regulated sizes and consistent shape. This technique ensures consistency and reproducibility in fiber properties by using a pre-made template or mold as a structural framework to direct the creation of nanofibers. Usually templates consist of porous membranes, molds, or scaffolds having nanoscale characteristics (Nam *et al*. 2014). They include silica-based materials, track-etched polycarbonate, or anodized aluminum oxide (AAO). A key benefit of template synthesis is the controllable dimensions of nanofibers such as their diameter, length, and aspect ratio. The precursor materials and processing settings can be adjusted. This technique enables the creation of nanofibers with intricate architectures, including hollow, core-shell, or segmented structures (Alghoraibi *et al*. 2018, Liu *et al*. 2020).

Template synthesis is used in material science and nanotechnology because of its accuracy and versatility. This exact structural control is crucial for ocular drug delivery because it guarantees uniform drug loading and release profiles. This is essential for treating bacterial infections, age-related macular degeneration, glaucoma, and other chronic eye disorders. The application of biodegradable polymers in template manufacturing increases its applicability (Uzel *et al*. 2023). Template manufacturing facilitates a combination therapy strategy by allowing several medications or therapeutic substances to be included into the nanofiber matrix (Garg *et al*. 2015).

2.1.3. Self-assembly

This process uses the forces and interactions between molecules in materials to create tiny structures on their own. This process creates nanofibers with proper structural control and functional properties. It uses some molecules' innate ability to arrange themselves into ordered structures. Molecular interactions such as hydrogen bonding, hydrophobic interactions, π-π stacking, electrostatic forces, and van der Waals contacts are necessary to the self-assembly process (Li *et al*. 2022). These forces cause molecules to spontaneously arrange themselves into distinct nanostructures. The first step in this process is to choose or design building blocks or molecules with specified functional groups (Mendes *et al*. 2017).

Self-assembled nanofibers have many benefits for ocular drug administration. They have the capacity to encapsulate hydrophilic and hydrophobic medications. This leads to increased stability and bioavailability. Self-assembly allows for precise control over the surface and structural characteristics of nanofibers (Song *et al*. 2021).

2.2. Nanofibers as potential delivery platform to overcome ocular barriers

The existence of various anatomical and physiological barriers is a major challenge in ocular drug delivery. These barriers prevent the transport of therapeutic agents to the target sites within the eye. Nanofiber-based drug delivery systems have emerged as a promising solution to address the issues associated with ocular drug delivery particularly for diseases like AMD (Uzel *et al*. 2023). Nanofibers provide substantial benefits in overcoming these obstacles. The tight junctions between the retinal endothelial cells, pigment endothelial cells restrict the movement of the drug. This barrier can be overcome by nanofiber drug delivery by enhancing the

solubility, stability, and bioavailability of the drug. The small diameter of the nanofibers allows its interaction with the cell membrane by increasing its permeability across blood-retinal barrier. The functionalized nanofibers bind to the receptors that are overexpressed in AMD-affected retinal tissues. This improves its localized delivery to retina (Omer and Zelkó 2021, Liu *et al*. 2023).

Cornea prevents drug penetration due to its dense, stratified epithelial layer. For ocular drug delivery to be effective, the drug must first pass through the pre-corneal and conjunctival barriers (Mun *et al*. 2014). Nanofibers can address this issue by being incorporated into eye. It ensures prolonged residence time on the ocular surface. The morphology of nanofibers fabricated by electrospinning ensures precise control of the diameter and surface properties. It allows for the fabrication of fibers that are small enough to permeate the corneal epithelium (Bachu *et al*. 2018).

Controlled release capabilities of nanofibers allow for the gradual release of therapeutic agents, maintaining effective concentrations in the target tissues over time. Controlled release quality is important for AMD as it is a chronic condition that requires long-term management. Nanofiber-based systems can be engineered to release the encapsulated drug over an extended period (Gaydhane *et al*. 2023, Vojoudi and Babaloo 2023).

3. Phytoconstituents for AMD: challenges and opportunities

Delivery methods based on nanofibers have many opportunities to improve therapeutic effectiveness of phytoconstituents in the management of age-related macular degeneration (AMD). In both cell and animal models it has been demonstrated that natural compounds such as retinol, anthocyanins, phenols, and other natural products shield the retina from oxidative stress. It also inhibits the development of new blood vessels. Natural materials show great promise for AMD treatment (Esentürk-Güzel *et al*. 2022). The regulated and sustained release of phytoconstituents is made possible by nanofiber-based delivery methods. It ensures long-lasting therapeutic effects and reduces systemic side effects. This subtopic explores the design, manufacturing processes, and possible uses of nanofiber-based delivery systems for phytoconstituent delivery for AMD (Chew *et al*. 2014) (Table 1).

Extensive research has been reported in literature, demonstrating efficacy of phytoconstituents like curcumin, quercetin, and resveratrol in the treatment of AMD. Phytoconstituents loaded nanofibers have shown promising results in the management of wound healing and cancer. Several researchers are exploring nanofibers as potential delivery platforms for phytoconstituents targeted for AMD mitigation.

Amer *et al*. developed PVA nanofibers loaded with Lepidium sativum extract which improved wound healing and showed the therapeutic value of phytochemicals when encapsulated in electrospun fibers. The nanofibers facilitate wound closure and stimulate fibroblast proliferation indicating their potential utility in tissue regeneration. The anti-inflammatory and antioxidant qualities of Lepidium sativum add to its medicinal effectiveness (Amer *et al*. 2022a). Mahmud *et al*. created electrospun fiber mats incorporating curcumin that has antibacterial and sustained release properties to increase the stability and bioavailability of phytoconstituents that are not very soluble in water (Mahmud *et al*. 2020). Bui *et al*. supported this strategy by formulating curcumin-loaded polycaprolactone-polyethylene glycol nanofibers. They improved cell adhesion and prolonged drug release which increased the effectiveness of wound healing (Bui *et al*. 2014).

Quercetin is a flavonoid which is known for its antioxidant and anti-inflammatory properties. Its therapeutic potential in wound healing applications has been studied. To improve quercetin's bioavailability and effectiveness, recent studies have focused on incorporating it into electrospun nanofibers. To produce an efficient wound dressing, Ajmal *et al*. functionalized electrospun nanofiber membranes with quercetin and ciprofloxacin hydrochloride. Incorporating quercetin improves the antibacterial activity of ciprofloxacin and it also offers antioxidant advantages. Ful-thickness wounds in in vivo preclinical trials showed faster healing (Ajmal *et al*. 2019b). Similarly Zhou *et al*. formulated electrospun nanofibers consisting of chitosan oligosaccharide/polycaprolactone loaded with rutin and quercetin. These nanofibers showed good antibacterial properties against common wound pathogens. The presence of quercetin enhances antioxidant activity which helps in mitigating oxidative stress at wound sites (Zhou *et al*. 2021).

In another study, Ajmal *et al*. fabricated biomimetic nanofibers composed of polycaprolactone and gelatin and incorporated ciprofloxacin hydrochloride and quercetin. These nanofibers exhibited robust antibacterial activity and good antioxidant properties. In vivo preclinical studies demonstrated accelerated healing in full-thickness wounds (Ajmal *et al*. 2019a). Nalini *et al*. explored the fabrication and evaluation of nanoencapsulated quercetin for wound healing applications. Encapsulating quercetin within nanofibers improves its stability and facilitates sustained release and enhances wound healing due to their antioxidant and anti-inflammatory properties (Nalini *et al*. 2023). Paolella *et al*. developed quercetin-encapsulated polycaprolactone-polyvinylpyrrolidone electrospun membranes intended for wound healing applications. The antioxidant properties of quercetin are preserved contributing to improved wound healing outcomes (Paolella *et al*. 2024).

Han *et al*. developed lutein-loaded polyvinyl alcohol/sodium alginate nanofibers using electrospinning techniques. Cross-linking duration highly influences the release rate. Nanofibers that were cross-linked for 1 hour exhibited a controlled release over an extended period. Those that were cross-linked for longer durations showed a decreased release rate (Han *et al*. 2019).

Varma *et al*. introduced a novel formulation of liposomal lutein using nanofiber weaving technology. Antioxidant potential of lutein was seen to be enhanced and improved in vitro release profiles. The integration of lutein with phospholipids preserves its bioactivity and facilitates a sustained release which is beneficial for maintaining therapeutic levels over time (Varma *et al*. 2021). Drosou *et al*. encapsulated β-carotene that is similar to lutein into food-grade nanofibers through coaxial electrospinning of hydrocolloids. Encapsulation enhances the oxidative stability and provides photoprotection to β-carotene (Drosou *et al*. 2022).

Table 1. Phytoconstituent's sources and their advantages for age-related macular degeneration.

Phytoconstituent	Sources	Potential benefits	MOA	References
Lutein and Zeaxanthin	Spinach, kale, corn, eggs	Antioxidant properties - Filters harmful blue light - Neutralizes free radicals - Slows AMD progression - Improves visual function	Lutein and zeaxanthin act as natural antioxidants in the macula of the eye, absorbing harmful blue light and preventing oxidative stress to maintain retinal health.	(Mrowicka et al. 2022)
Anthocyanins	Blueberries, blackberries, cherries	Antioxidant properties - Anti-inflammatory effects - Protects retinal cells from oxidative stress and inflammation - Reduces risk of AMD progression	Anthocyanins are potent antioxidants that scavenge free radicals and decrease inflammation in retinal tissues, therefore protecting against the oxidative damage and inflammation associated with AMD development.	(Huang et al. 2018)
Polyphenols	Grapes, red wine, green tea, apples, onions, berries	Antioxidant properties - Anti-inflammatory effects - Protects retinal cells and blood vessels - Reduces risk of AMD progression	Polyphenols contain antioxidant and anti-inflammatory effects, which neutralize free radicals and reduce inflammation in retinal tissues. This preserves retinal cells and blood vessels, reducing the risk of AMD formation.	(Caban and Lewandowska 2021)
Omega-3 fatty acids	Fatty fish (salmon, mackerel, sardines), flaxseeds, walnuts	Anti-inflammatory effects - Maintains retinal health - Reduces risk of advanced AMD	Omega-3 fatty acids have anti-inflammatory properties that help to reduce inflammation in the retina, preserve retinal health, and reduce the chance of developing severe AMD by regulating the inflammatory pathways that drive disease progression.	(Singer et al. 2008)
Curcumin	Turmeric	Antioxidant properties - Anti-inflammatory effects - Protects retinal cells from oxidative stress and inflammation – Anti-angiogenic properties.	Curcumin's antioxidant and anti-inflammatory effects reduce inflammation in retinal tissues protecting against oxidative damage and AMD development.	(Franzone et al. 2021, Allegrini et al. 2022)
Vitamin C and E	Citrus fruits, kiwi, almonds, sunflower seeds	- Antioxidant properties - Protects retinal cells from oxidative damage - Supports overall eye health - Reduces risk of AMD development or progression	Vitamins C and E are antioxidants that neutralize free radicals and protect retinal cells from oxidative damage, so enhancing overall eye health and decreasing the risk of AMD development or progression.	(Beatty et al. 2000)
Ginkgo biloba	Ginkgo biloba extract	Potential neuroprotective effects - Some improvement in visual function in early-stage AMD	Ginkgo biloba may have neuroprotective properties, protecting retinal cells from damage, and it may enhance visual function in early-stage AMD, most likely via increasing blood flow to the retina and improving neuron survival.	(Sofi et al. 2020)

Phytochemicals such as fig latex, lupeol, curcumin, polyphenols and quercetin have strong antioxidant, anti-inflammatory and anticancer properties. Their poor bioavailability, stability and rapid degradation affect their therapeutic efficacy. Recent studies have electrospun nanofibers as advanced delivery platforms to overcome these challenges.

El Fawal *et al*. formulated fig latex-loaded cellulose acetate/poly(ethylene oxide) nanofibers that show anticancer activity against colon and liver cancer cells (El Fawal *et al*. 2024). Similarly lupeol-incorporated polycaprolactone (PCL)/gelatin nanofibers developed by Ravichandran and Radhakrishnan exhibited controlled lupeol release ~80% in 40 hours suggesting their potential for prolonged anticancer effects (Ravichandran and Radhakrishnan 2022).

Beyond anticancer applications, Sampath *et al*. studied curcumin-loaded PLGA nanofibers which exhibited strong growth inhibition of carcinoma cells (Sampath *et al*. 2014). Meanwhile, Kim *et al*. proved that polyphenol-loaded PCL nanofibers inhibit human cancer cell proliferation supporting the broad-spectrum cytotoxic potential of phytochemical-loaded nanofibers (Kim *et al*. 2012).

In dermatological applications, Amer *et al*. encapsulated quercetin into electrospun nanofibers for acne treatment and showed antibacterial properties and reduction of acne lesions (Amer *et al*. 2022b).

Compared to synthetic drugs, designing delivery systems for phytoconstituents using nanofibers has numerous hurdles. This is because of their complex chemical structures, poor

solubility, and stability issues. Phytoconstituents often require hydrophilic polymer matrices or bioenhancers to improve solubility and absorption whereas synthetic drugs have well-defined pharmacokinetics and are easier to formulate (Uddin *et al*. 2024). Since many chemicals produced from plants are prone to degradation, controlled release mechanisms are essential for maintaining bioactivity in nanofiber formulations for phytoconstituents. In contrast synthetic drugs can often rely on standardized encapsulation techniques and targeting strategies such as ligand-functionalized nanofibers. Phytoconstituents can benefit from nanofiber-based delivery by providing sustained release, localized delivery, and reduced dosing frequency which are crucial for treating chronic conditions like AMD (Tomar *et al*. 2023).

3.1. Challenges in delivering phytoconstituents

There are various obstacles in the way of delivering phytoconstituents for age-related macular degeneration (AMD). Numerous phytoconstituents, including terpenoids, flavonoids, curcumin, and resveratrol have limited bioavailability and poor water solubility which restricts their potential as therapeutic agents. The many barriers in the eye such as the retinal layers, stroma, and corneal epithelium make these problems worse by preventing drugs from penetrating. Furthermore, nasolacrimal drainage and tear turnover frequently cause phytoconstituents to be quickly removed from the ocular surface requiring repeated administration. The highly reactive environment of tissues damaged by AMD might break down these substances decreasing their efficacy and stability (Pokkalath *et al*. 2022, Krishnaswami *et al*. 2024).

The corneal epithelium and blood-retinal barrier are two of the eye's defense mechanisms. They prevent substances from reaching the retinal tissues. As a result, it becomes difficult to achieve therapeutic concentrations at the target site. This lowers the effectiveness of phytochemicals in treating AMD (Adelli 2013).

Nanofiber systems offer higher bioavailability. A higher percentage of therapeutic phytoconstituents reach the intended tissues in the eye. It improves the effectiveness of treatment. Therapeutics can be precisely localized to particular cells or tissues in the AMD-affected eye using nanofiber-based delivery devices that can be tailored for targeted administration. This increases therapeutic efficacy while lowering off-target effects. Tailored nanofibers allow for the gradual release of phytoconstituents. This preserves therapeutic concentrations in the eye and lowers the need for frequent delivery (Mendes *et al*. 2017). Nanofiber-based methods offer a way to reduce the exposure of the entire body to therapeutic drugs. It reduces the possibility of systemic side effects normally linked to earlier delivery methods. Combination treatment is effective in addressing the complicated nature of AMD development because of the versatility of nanofiber-based delivery methods. It also allows for the inclusion of a wide range of drugs (Torres-Martinez *et al*. 2018). This results in better therapeutic outcomes. Researching the use of nanofiber-based delivery methods to supply phytoconstituents in AMD therapy appears to be a viable choice for enhancing patient adherence, safety, and efficacy in managing this eye-threatening condition (Alam *et al*. 2023) (Table 2).

4. Nanofibrous carriers for AMD

Various techniques are used to incorporate phytoconstituents into nanofiber matrix. For improved delivery in the treatment of AMD. Encapsulation within nanofibers enhances stability and bioavailability. It ensures uniform dispersion of bioactive substances like quercetin or curcumin throughout the matrix. Nanofiber surfaces can be conjugated with ligands or mucoadhesive polymers. This improves contact with ocular tissues and receptors overexpressed in AMD to allow targeted delivery (Satchanska *et al*. 2024). Coaxial electrospinning makes it easier to create core-shell nanofibers by adding a protective polymer shell around the phytoconstituent-containing core. This ensures the regulated release and extended retention of therapeutic drugs such as curcumin or resveratrol on ocular surfaces. When combined, these strategies maximize the effectiveness of drug administration which may improve therapeutic results in the treatment of AMD (Han and Steckl 2019).

Garkal *et al*., focused on developing lutein-loaded nanofibers to treat AMD. In vitro drug release studies showed a sustained release of 81.75% over 25 days. The antioxidant properties of lutein were preserved in the nanofibers. The nanofibers showed good stability under accelerated conditions for 6 months. The in vivo preclinical studies indicated the biocompatibility of the thin-film device. Large-scale production is possible by the industrial scalability of the electrospinning processes (Garkal *et al*. 2022) (Figure 2).

Additional phytoconstituents with anti-inflammatory and antioxidant qualities can be included in nanofibers. To address inflammation and oxidative stress in AMD. It is possible to co-load many phytoconstituents into nanofibers. This results in a combination therapeutic action that improves retinal protection. By treating angiogenesis and oxidative damage at the same time, this technology can be used to provide a combination of phytoconstituents with traditional medications like anti-VEGF medicines. This offers a synergistic approach to AMD treatment (Figure 3).

Nanofibers enable targeted distribution to retinal regions, sustained release, and increased bioavailability. For wound healing, Karuppannan *et al*. created quercetin-loaded polycaprolactone (PCL)/gelatin (GLN) electrospun nanofibers that showed biocompatibility and sustained drug release while promoting fibroblast growth (Karuppannan *et al*. 2022).

Table 2. Examples of nanofiber-phytoconstituent combinations.

Phytoconstituent	Nanofiber material	Application	References
Curcumin	Polycaprolactone (PCL)	Wound Healing, Anti-inflammatory	(Ranjbar-Mohammadi et al. 2016)
Quercetin	Poly(lactic-co-glycolic acid) (PLGA)	Wound Healing, Antioxidant	(Alves et al. 2020)
Epigallocatechin gallate (EGCG)	Poly(vinyl alcohol) (PVA)	Antimicrobial, Antioxidant	(Tan et al. 2023)
Essential Oils	Polyethylene oxide (PEO)	Antimicrobial, Drug Delivery	(Lin et al. 2017)

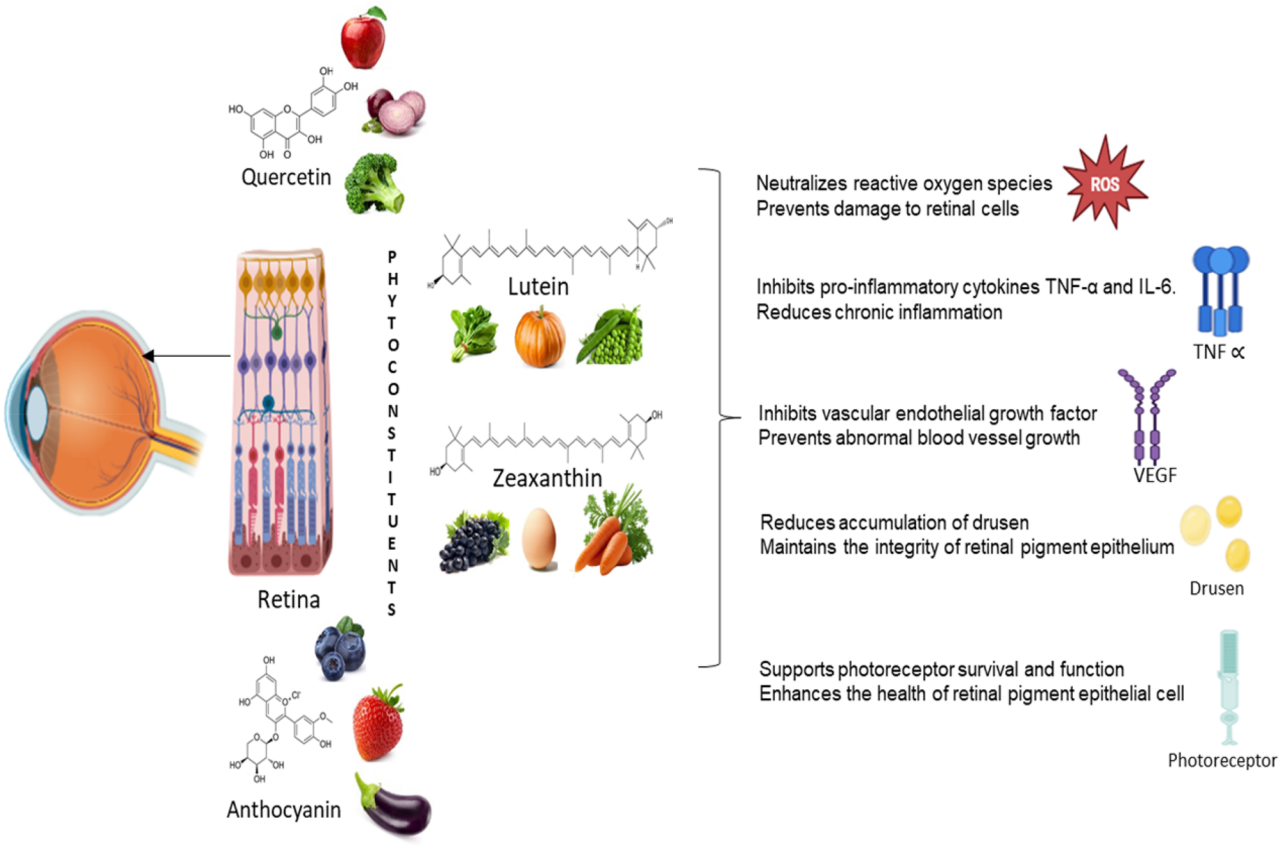

Figure 2. Mechanisms of phytoconstituent action in AMD. Phytoconstituents such as quercetin, lutein, zeaxanthin, anthocyanin, etc. exert their therapeutic activity using mechanisms such as antioxidant activity, anti-inflammatory effects, and anti-angiogenic properties (Adelli 2013, Bungau et al. 2019) (created with Biorender.com).

De Souza *et al*. displayed that core-shell electrospun nanofibers with a PVA core and a PCL/gelatin shell sustained bevacizumab release over 6 days while preserving its antiangiogenic properties. Nanofibers present a viable method for the controlled administration of bevacizumab which could decrease the frequency of intravitreal injections required for the treatment of AMD (de Souza *et al*. 2018). Another group also developed nanofiber-coated intravitreal implants for dual-drug delivery of bevacizumab and dexamethasone achieving 88% bevacizumab release within 48 hours and sustained dexamethasone release over 35 days (Guerra *et al*. 2023). For targeted drug delivery in the vitreous cavity, Silva *et al*. created polycaprolactone nanofibers of dexamethasone acetate. In vivo preclinical testing in rats confirmed biocompatibility. In vitro drug release experiments showed continuous dexamethasone diffusion over 10 days. This findings show prolonged corticosteroid treatment for retinal illnesses using nanofiber-based drug delivery while maintaining ocular safety (Da Silva *et al*. 2019). These studies collectively show the potential of electrospun nanofibers for sustained ocular drug delivery. They prove the controlled release of bevacizumab and dexamethasone while ensuring biocompatibility and retinal safety in preclinical models.

Taghe *et al*., Mehrandish *et al*., and Göttel *et al*. created electrospun nanofibers. In preclinical testing on rabbit models, Taghe *et al*. showed that ketorolac tromethamine nanofibrous inserts significantly increased drug exposure obtaining a 6- to 8-fold increase in comparison to eye drops while sustaining a prolonged release for 140 hours (Taghe *et al*. 2024). Mehrandish *et al*. developed polymeric nanofibers with good antifungal action, a 55-day controlled drug release and excellent biocompatibility for prolonged antifungal itraconazole release. In an ex vivo pig eye model Göttel *et al*. confirmed their gellan gum/pullulan-based nanofiber system's rapid gelation and prolonged ocular retention (Göttel *et al*. 2020, Mehrandish *et al*. 2022).

4.1. Safety and toxicity profile of the phytoconstituents

Nanofiber materials' biocompatibility is essential to their successful application in healthcare and biological fields. This means selecting biocompatible polymers that break down into nontoxic by-products while matching tissue regeneration rates, such as PLGA, PCL, collagen or chitosan (Berdimurodov *et al*. 2023). For catering nanofibers in case of AMD, biocompatibility mainly refers to the ocular tissues present especially in the retina and blood-retinal barrier. Fabricating nanofibers using biocompatible and biodegradable nanofibers ensures there is no accumulation in the retinal tissues which might be the cause of inflammation in retina, stress to the cells and eventually leading to cell death due to toxicity. This further activates innate immune response and releases pro-inflammatory cytokines which leads to potential disruption of retinal integrity. Since nanofibers are recognized as foreign particles by the host's immune system, it might lead to inflammatory response; but the surface properties like

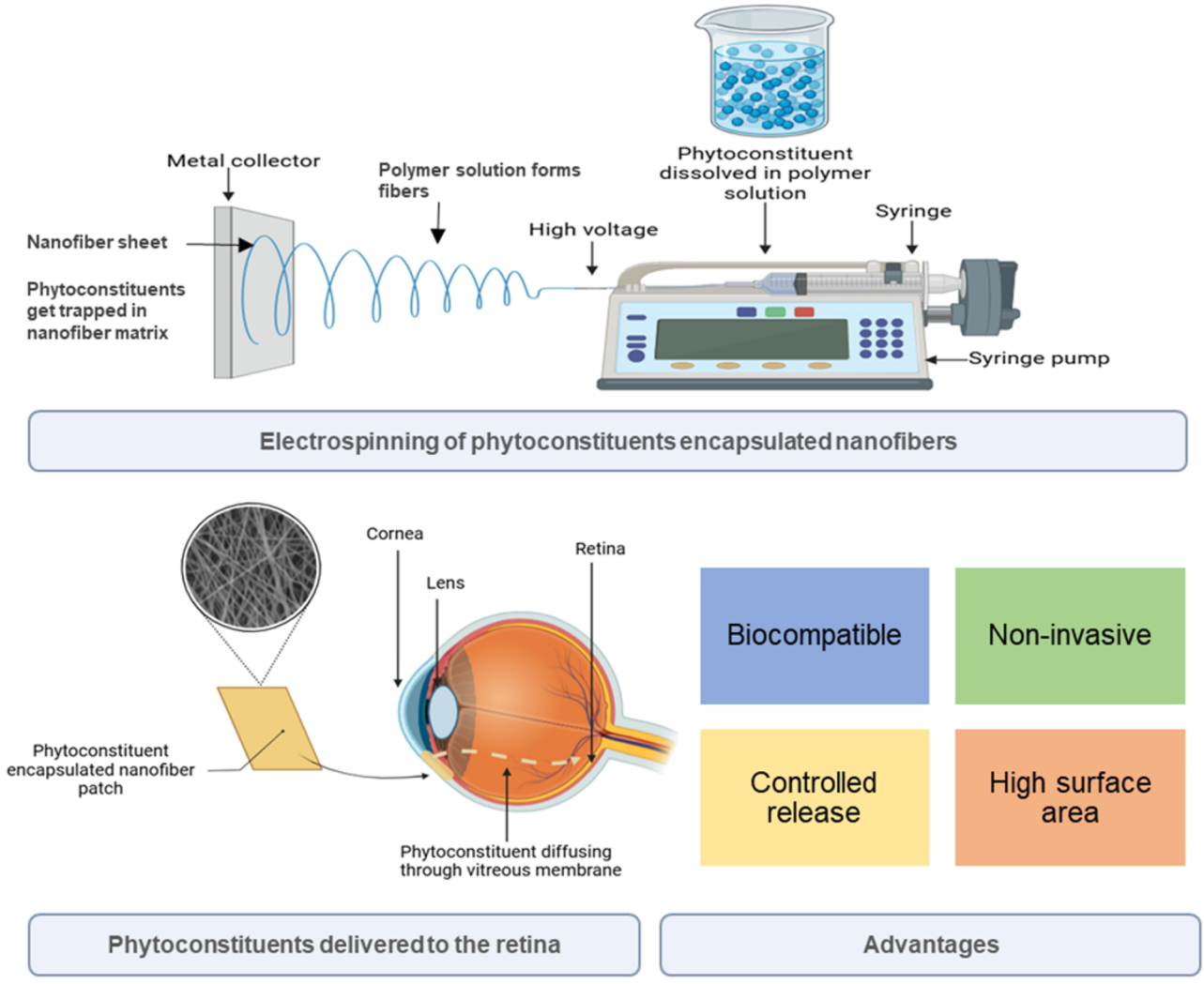

Figure 3. Nanofiber-based drug delivery system for AMD. Nanofibers encapsulate phytoconstituents and deliver them to the retina (Torres-Martinez et al. 2018) (created using Biorender.com).

charge, hydrophilicity, porosity, influence cellular uptake and biodistribution ensuring these interactions do not lead to cytotoxicity. The long term use of nanofibers on ocular tissues could cause damage overtime even after therapeutic effect has been achieved. Prolonged exposure to nanofibers could result in chronic inflammation in retina due to an immunogenic response.

Preclinical studies are necessary to ensure that nanofiber materials are safe for clinical application. It is also important to confirm biocompatibility and regulatory compliance. Resolving these problems leads to formulation of nanofiber materials with enhanced biocompatibility. When using nanofiber materials, minimizing potential negative effects on ocular tissues requires efforts. Choosing biocompatible polymers which are safety in ocular applications, such as polyethylene glycol (PEG) or poly(lactic-co-glycolic acid) (PLGA), is necessary (Osi *et al*. 2022). Using cell-adhesive peptides or bioactive compounds for surface modification method can improve ocular tissue integration while lowering foreign body reactions. It is important to use ethylene oxide and gamma irradiation cautiously to prevent altering the material's characteristics. It also helps to leave behind potentially dangerous residues. Control of the nanofiber particle size and shape is necessary to avoid irritation of ocular tissues. Proper drug release kinetics is necessary to maintain therapeutic doses while preserving the integrity of ocular tissue. In vivo animal studies are required to accurately assess biocompatibility, ocular safety and performance. The safe and effective use of nanofiber materials in ocular applications is ensured by compliance with safety regulations established by the FDA or ISO (Batur *et al*. 2024). Shirsath *et al*. analyzed the information that was available on the use of plants. They studied their biological origins, active phytochemical components and the mode of activity of different pharmacological classes. According to the study, phytoconstituents present a viable substitute for synthetic medications. They reduce adverse effects and ensure high efficacy and enhanced patient adherence. The authors also stressed the efficacy and safety of drug delivery methods based on herbs in the treatment of a number of illnesses (Shirsath and Goswami 2020).

The clinical translation of nanofibers for laboratory scale to clinical applications involve overcoming various challenges related to regulatory approval form the agencies such as USFDA and EMA. The nanofiber-based therapies need to

undergo extensive Phase I to Phase III trials including studies on the dosing, pharmacokinetics, drug release profiles, its long-term effects and potential side effects. The degradation products of the biodegradable polymer are of paramount importance. The safety of the raw materials also needs to be verified through rigorous testing for cytotoxicity, genotoxicity and immunogenicity. But among all these one of the critical challenges in gaining the regulatory approval is the ensuring batch to batch consistency in the production and resolving issues pertaining to its stability since nanofibers can have variable properties like size, shape, surface charge, porosity, etc. The complexity and the cost manufacturing is considered to be a significant barrier as the specialized equipment required in case of electrospinning increased the production cost. Lowering manufacturing cost through advances in nanomaterial synthesis and large-scale production is vital for future of nanomaterial based treatments. The stability issues can arise due to several factors which include various factors like pH, temperature, ionic strength resulting in inconsistent drug release profiles. There are chances that a burst release of drug from nanofibers resulting in suboptimal therapeutic levels of drug; conversely a slow degrading nanofiber matrix may persist in tissue for a longer duration of time might further lead to local toxicity. In some cases, nanofibers form aggregates especially in aqueous solutions leading to loss of uniformity and impaired drug release.

5. Strategies to overcome ocular barriers with nanofibrous carriers

Innovative techniques include surface functionalization for improved drug targeting. Mucoadhesive polymers increase retention time. Stimuli-responsive nanofibers allow for regulated drug release. These strategies are used to permeate across ocular barriers with nanofibrous carriers. They address the issues of tear drainage restricted permeability and intricate ocular anatomy. These strategies provide efficient and long-lasting medication administration to the eye.

5.1. Surface functionalization

Surface functionalization is the process of altering the surface properties by attaching polymers, chemical groups or other elements. By interacting with ocular tissues, functionalized nanofibers can enhance localized delivery. Customized surface characteristics make it easier to get through ocular barriers (Wieszczycka *et al*. 2021). According to a review by Yoo *et al*. surface functionalization of nanofibers is crucial for improving their performance and adaptability in biomedical applications. The article describes a number of surface functionalization techniques, including: By adding functional groups to the nanofibers' surface, plasma treatment enhances their ability to interact with biological substances. By chemically attaching functional groups to the surface, wet chemical methods improve cell adhesion and biocompatibility. Graft on the Surface One method for fine-tuning characteristics including hydrophilicity, mechanical strength, and drug release patterns is polymerization, which involves grafting polymers onto the surface of nanofibers (Yoo *et al*. 2009). Kolambkar *et al*. looked into the effects of surface functionalization with a collagen-mimicking peptide (GFOGER). Nanofiber orientation was performed on human mesenchymal stem cells (hMSCs). The researchers discovered enhanced bone cell differentiation, migration and proliferation on the nanofibers. Random fibers did not have the same effect as aligned nanofibers, which directed cells to migrate in a particular direction. Aligned fibers and the peptide coating improved cell growth and migration. The study demonstrated that surface functionalization and fiber orientation are helpful for tissue regeneration (Kolambkar *et al*. 2014).

Similarly, surface functionalization of nanofibers in age-related macular degeneration (AMD) can be used to enhance drug delivery by improving cellular uptake, stability and targeting.

5.2. Mucoadhesive nanofibers

Mucoadhesive nanofibers are nanofibers with adhesive qualities that enable them to stick to mucosal tissues like the mouth, nose, gastrointestinal system or eye. Adding particular polymers or molecules that can interact with the mucus layer or mucosal tissue. Examples of these polymers are chitosan, hydroxyl propyl methyl cellulose, polyvinyl alcohol, etc. They provide mucoadhesive property. They also improve adhesion and extends the nanofiber retention period at the application site. First-pass metabolism is avoided. Mucoadhesive nanofibers might be used to deliver therapeutic substances more successfully. Mucoadhesive nanofibers can improve the treatment of AMD and other retinal disorders by delivering medications straight to the eye in the form of patches or films. These mucoadhesive qualities enable them to adhere to the mucosal surface, enabling regulated and extended medication release (Pérez-González *et al*. 2019).

Cegielska *et al*. investigated the fabrication of mucoadhesive electrospun nanofibers as a substitute medication delivery method for the treatment of glaucoma. Brinzolamide was used as the anti-glaucoma drug. The researchers created a nanofibrous delivery system of polycaprolactone, hydroxypropyl cellulose and β-cyclodextrin. The results demonstrated that the β-cyclodextrin/brinelamide interactions enabled the successful incorporation of the drug into the nanofibers, resulting in more precise dosage (Cegielska *et al*. 2022). A study by Çağlar *et al*., examined the development of innovative mucoadhesive electrospun nanofibrous ocular inserts (OS) that deliver the antibiotic moxifloxacin to the eye under regulated conditions. The inserts showed antibacterial qualities for treating eye infections. Regulated release behavior was demonstrated (Çağlar *et al*. 2025).

5.3. Stimuli-responsive nanofibers

Stimuli-responsive nanofibers for ocular distribution react to particular external stimuli like variations in temperature, pH, ionic strength and electro conductivity. They release medications at the targeted location inside the eye. The nanofibers incorporate polymers that when exposed to specific stimuli, change

chemically or physically. Thermosensitive polymers come into contact with the eye and change from a sol to a gel state at physiological temperatures. This helps to extend drug retention and allow for controlled release. The pH of the ocular environment cause pH-sensitive polymers to alter their structure or break down. Thus medication is released locally. Polyethylene glycol (PEG), poloxamers, poly(lactic-co-glycolic acid) (PLGA), chitosan, hyaluronic acid and poly(N-isopropylacrylamide) (pNIPAAM) are common polymers of stimuli-responsive ocular nanofibers. These polymers used in ocular drug delivery systems because they are biocompatible, biodegradable and have the capacity to control drug release (Berillo *et al*. 2021). Pandit *et al*., developed fenofibrate-loaded nanofibers (FenoNF) integrated into a thermoresponsive in-situ gel for ocular administration to target the posterior portion of the eye. Fenofibrate has low aqueous solubility but is useful to treat neovascular ocular disorders. The gel demonstrated consistent drug release upto 24 hours (Pandit *et al*. 2023).

5.4. Nanofiber crosslinking

It is possible to use crosslinking agents such glutaraldehyde, ethylenediamine, genepin, citric acid, etc. to increase the mechanical strength and stability of nanofibers. Crosslinking improves the formulation's stability and prolongs its shelf life. They prevent the nanofibers from breaking down early. Grimaudo *et al*. created electrospun hyaluronan nanofibers using peptide ε-polylysine as an antibacterial. Crosslinking the nanofibers with ε-polylysine improves stability and regulates drug release. Crosslinking with ε-polylysine is a crucial strategy to improve the mechanical properties and endurance of the nanofibers and assist them in overcoming ocular barriers including short residence durations and early disintegration (Grimaudo *et al*. 2020).

6. Future perspective and challenges

Nanofibers show good promise to advance medical application in drug delivery. Their usefulness in treating age-related macular degeneration (AMD) allows for the regulated, targeted release of bioactive substances. They have the potential to completely alter existing therapy approaches. Herbal bioactives have been included into a number of therapeutic treatments. Due to issues like inconsistent potency, poor water solubility and low stability, their efficacy has been limited. The incorporation of bioactive compounds into nanofiber-based drug carrier systems prevents these problems. They enhance the stability and bioavailability of therapeutic medicines. They also permit fine control over their release dynamics.

Innovative methods for isolating and characterizing therapeutically active ingredients from medicinal plants are required to effectively utilize the potential of herbal bioactives in such systems. Standardized extraction methods that guarantee known potency and reproducibility are essential or to create formulations that can satisfy the exacting standards of regulatory agencies. Choosing the right nanofiber matrix system is essential for customizing medication release characteristics. Formulations may need immediate or sustained release patterns, depending on the therapeutic needs, and the matrix material is essential to obtaining these results (IJPSR, XXXX).

Bioactive substances derived from plants is necessary to prolong the shelf life of formulations based on nanofibers. They improve product stability and scalability. It is recommended to switch from using crude extracts to refined natural ingredients. Purified bioactives ensure predictable therapeutic results. They are more consistent and compatible with nanofiber systems. Ocular drug delivery systems based on nanofibers have enormous potential for the focused and long-term treatment of diseases like age-related macular degeneration (AMD). They must overcome several regulatory obstacles before they can be used in clinical settings. These assessments are essential for upholding scientific integrity in regulatory decision-making. It supports the FDA's objective of promoting technological innovation. It is also necessary to safeguard public health. Particularly when addressing delicate organs like the eye, regulatory bodies like the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) demand strong proof of safety and manufacturing quality for treatments based on nanotechnology (Uddin *et al*. 2024).

Preclinical studies to assess biocompatibility and toxicity is required for nanofiber systems. Potential hazards include irritation, inflammation and immunological reactions. In vitro and in vivo studies are required by regulatory requirements to evaluate eye irritation and biodegradability. Nanofiber breakdown products need to be nontoxic and show long-term compatibility with ocular tissues. Studies also need to assess the possibility of interactions with ocular barriers including the cornea and retina as well as off-target effects. Clinical trials for ocular systems based on nanofibers have to follow strict guidelines, such as Good Clinical Practice (GCP) guidelines. Special emphasis should be given to drug retention, release profiles and possible side effects. Large patient groups are necessary for later-phase trials (Phase III) to verify long-term safety and efficacy. In order to meet regulatory requirements for sterility, homogeneity and product stability, developers must also offer validated processes for consistent production that guarantee scalability and reproducibility (Romeo *et al*. 2023).

Products are subject to different regulatory frameworks. The FDA modifies its methodology to account for these variations. It helps to ensure an accurate evaluation of safety and effectiveness through a customized review procedure. With the help of thorough study and testing, the FDA monitors the market continuously after clearance to ensure adherence to safety and legal requirements. This ongoing monitoring guarantees that goods based on nanotechnology satisfy legal specifications (Foulkes *et al*. 2020). Emerging technologies like 3D printing nanofibers have a revolutionary potential to improve the treatment of age-related macular degeneration (AMD). 3D printing offers more exact spatial control than standard electrospinning methods. It creates nanofiber scaffolds with individualized topologies, porosities, and diameters to meet particular therapeutic demands, in applications involving the eyes, where highly specialized drug delivery systems are necessary due to the intricate anatomy of the eye, this feature is very beneficial.

It may be possible to create drug delivery systems or implants tailored to a patient. This can be done by

combining 3D printing with the formulation of nanofibers. This may create scaffolds that gradually deliver drugs and phytoconstituents to the retina. Steady drug concentrations at the target location can be made possible. It reduces systemic exposure and adverse effects. 3D-printed nanofibers could have several zones or layers with different purposes. It can include an interior layer for long-term medication release and an outside layer for protection to improve ocular compatibility. These developments make it easier to incorporate stimuli-responsive components. This empowers the release of drugs in reaction to particular triggers, like pH shifts or enzymatic activity in AMD-affected tissues (Elshabrawy *et al*. 2024). This collaboration could introduce novel regenerative treatments that focus on disease regulation and retinal regeneration. Obtaining exact control over nanofiber morphology and drug loading remains difficult. This makes the development of nanofiber-based drug delivery systems extremely difficult. Other challenges with ocular delivery include overcoming immunological and physical defenses while reducing discomfort. Techniques include using biocompatible materials and altering the surface can improve the security and efficacy of these systems (Suleman *et al*. 2021).

Customization of these systems to maximize therapeutic success and minimize side effects is possible by utilizing patient-specific genetic, molecular, and disease-related characteristics (Jin and Zhang 2023). Its main benefit is the versatility of nanofiber technology with regard to scaffold construction, release kinetics, and drug content. It may be possible to create nanofibers to address the vast variations in AMD therapy response and disease progression among individuals (Kirkova *et al*. 2022). Genetic testing may reveal particular biomarkers or mutations linked to the advancement of AMD. It allows for the incorporation of customized therapeutic agents into the nanofiber system. Antioxidants, anti-VEGF medications or compounds that silence genes can be used. This minimizes systemic exposure and adverse effects by guaranteeing that medication release is restricted to and activated in sick tissues. The rate of disintegration of nanofiber scaffolds could be tailored to each patient's treatment plan. It enables periodic or continuous drug delivery according to their therapeutic requirements. It is also possible to combine several medicines on a single platform with personalized nanofiber systems. Nanofibers filled with more than one drug can provide synergistic therapy for patients with coexisting ophthalmic diseases. Combining nanotechnology with genetics provide a platform for advancing in precision medicines.

7. Conclusion

Natural substances like retinol (vitamin A), anthocyanins (found in fruits like blueberries), phenolic compounds and other antioxidants are among the most promising novel approaches for treating AMD. It is well recognized that these bioactive compounds can prevent angiogenesis, which is the growth of new, aberrant blood vessels that leads to wet AMD. They have strong antioxidant properties that help in shielding retinal cells from oxidative stress. Oxidative stress is a major contributing cause to the development of AMD. There are a number of issues that restrict the efficacy of these drugs when delivered through traditional methods. They are poor solubility, quick degradation and low bioavailability. These limitations affect their clinical use.

This is where drug delivery technologies based on nanofibers are useful. Nanofibers are made using methods like electrospinning. Nanofibers have the ability to encapsulate bioactive substances. This enhances their solubility, bioavailability and protects them from degradation. Nanofiber's high surface area improves therapeutic absorption and dissolution of drugs. This results in more effective and prolonged drug delivery to the target tissues. This is especially crucial for AMD since the nanofibers can be made to target the retinal tissue in a specific way, releasing the therapeutic chemicals gradually over time. Nanofibers release drugs in a regulated and sustained manner. They are thus useful for treating AMD. This is important since AMD frequently necessitates long-term treatment plans in order to limit the disease's progression. It is possible to carefully regulate the release of natural substances such as retinol and anthocyanins using nanofibers, guaranteeing that their levels in the eye stay constant at effective quantities. Continuous release gives patients a less intrusive and more convenient treatment choice by reducing the frequency of administration.

Surface functionalization of nanofibers improve their capacity to permeate through ocular barriers like the layers of the cornea and retina. The specificity and effectiveness of drug delivery to the retina can be greatly increased by surface modifications, such as the addition of targeting ligands (such as antibodies or peptides). These ligands identify receptors that are overexpressed in tissues damaged by AMD. Targeted distribution maximizes the therapeutic benefit while reducing the possibility of systemic side effects. It is also possible to combine several therapeutic medicines on a single platform utilizing nanofiber-based drug delivery devices. Combining antioxidants, anti-angiogenic medicines and gene therapy techniques for treatment of AMD improves treatment results. 3D printing technology can be used in conjunction with nanofiber-based systems to create customized medicine delivery devices that are suited to each patient's particular requirements. It is possible to tailor 3D-printed nanofiber scaffolds to deliver a particular combination of bioactives. It provides a more customized strategy that can be adjusted to the requirements of each patient. Nanofiber-based systems must go through a number of crucial stages before its commercialization. This is necessary to guarantee the safety, effectiveness, scalability and regulatory compliance of the treatment. It is necessary to choose the right polymers to enhance drug encapsulation and release profiles.

Although this review primarily discusses the application of nanofibers, phytoconstituents and strategies for overcoming ocular barriers in the treatment of Age-Related Macular Degeneration, it is important to note that these approaches have broader implications in the field of drug delivery. The strategies outlined for targeting the ocular environment are also being explored in the treatment of other diseases such as cancer and diabetes where overcoming biological barriers remains a challenge. However given the unique challenges of the ocular environment in AMD, the methods discussed here are particularly valuable for enhancing the targeted delivery of therapeutics to the retina. These advances in drug delivery systems not only hold promise for AMD but also provide a foundation for addressing similar challenges in other therapeutic areas.

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All authors contributed to the study's conception, design, data analysis, and interpretation. Ulia Andrades, Sahil Gaikar, and Khushali Nathani were responsible for drafting the manuscript. Sujata Sawarkar and Abdelwahab Omri supervised the study, critically revised the manuscript for intellectual content, and provided final approval for publication. All authors have read and agreed to the final version of the manuscript and meet the criteria for authorship as per the ICMJE guidelines.

Authors contributions

CRediT: **Ulia Andrades**: Methodology, Writing – original draft; **Sahil Gaikar**: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing; **Khushali Nathani**: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing; **Sujata Sawarkar**: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Validation, Visualization, Writing – original draft, Writing – review & editing; **Abdelwahab Omri**: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – review & editing.

Consent for publication

All authors have provided their consent for publication.

Conceptualization and design

U. Andrades; Interpretation of data: S. Gaikar and K. Nathani; Writing - Drafting and editing: U. Andrades, S. Gaikar, K. Nathani and S. Sawarkar; Review: S. Sawarkar and A. Omri, A. Omri; Supervision: S. Sawarkar and A. Omri. All authors have read and agreed to the final version of the manuscript and meet the criteria for authorship as per the ICMJE guidelines.

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