

Oxysterols and Aldose Reductase Inhibitors as Non-Surgical Treatments for Cataracts



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Global Impact

- 45-51% of cases of blindness in the world are caused by cataracts (Pesudovs et al. 2024)
- Over half of all Americans develop at some point by age 80, but most are able to get it treated via surgery (Asbell et al. 2005)
- Cataract surgery is a very safe and effective procedure but requires access to resources such as adequate healthcare facilities, surgeons, etc. (Atima et al. 2024)
- 94 million people suffer some level of vision impairment due to the disease, with 90% of them living in low- and middle-income countries where resources for cataract surgery are limited (Cicinelli et al. 2023)
- This literature review explored emerging non-surgical treatments as accessible alternatives to cataract surgery

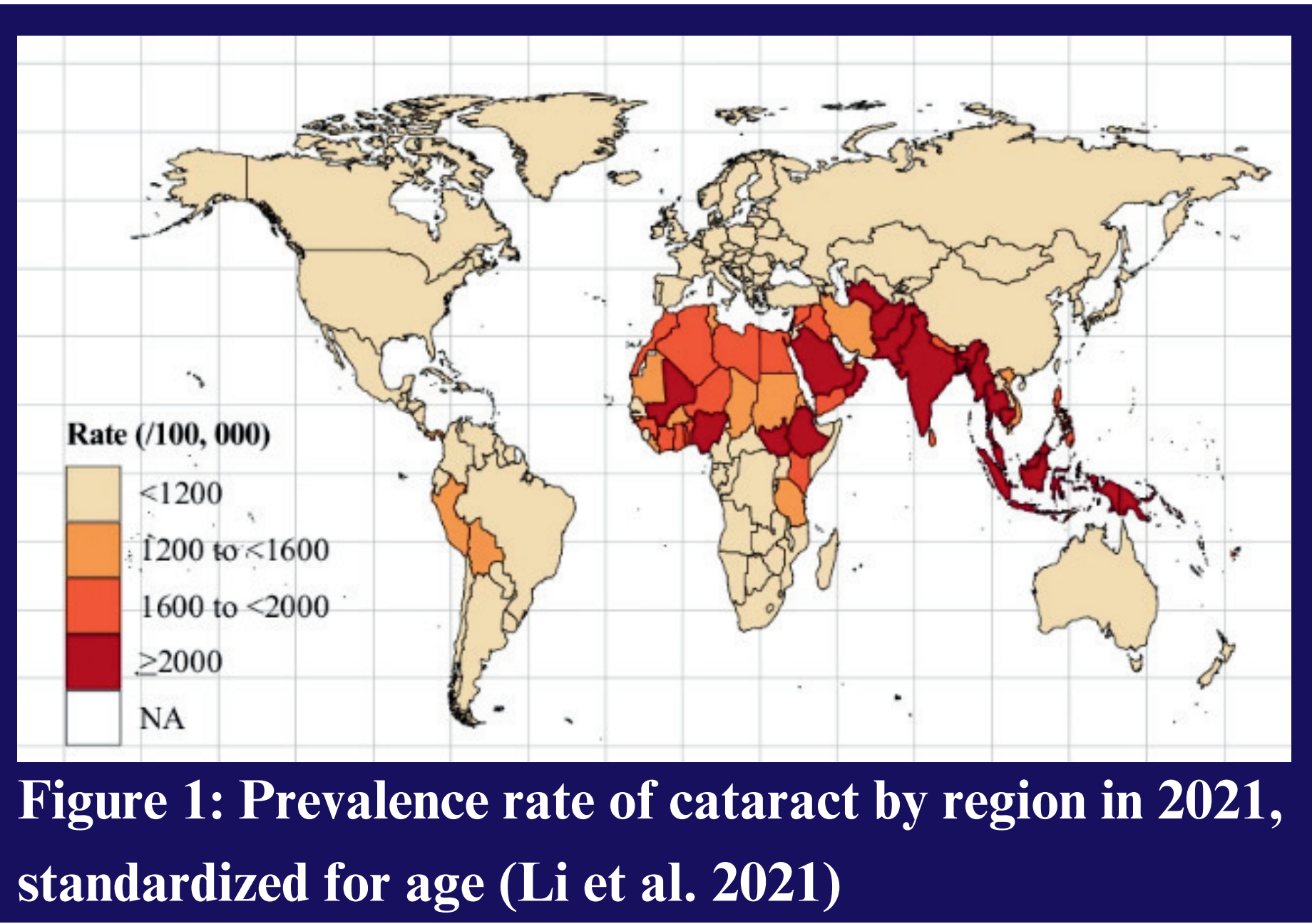


Figure 1: Prevalence rate of cataract by region in 2021, standardized for age (Li et al. 2021)

Oxysterol VP1-001

- A derivative of cholesterol, it has been proposed as a treatment in the hope that it can target and bind to α -crystallin proteins returning them to their native state (Makley et al. 2015)
- This prevents aggregation of α -proteins, but also restores their role as chaperones that inhibit other lens proteins from aggregating (Molnar et al. 2019)

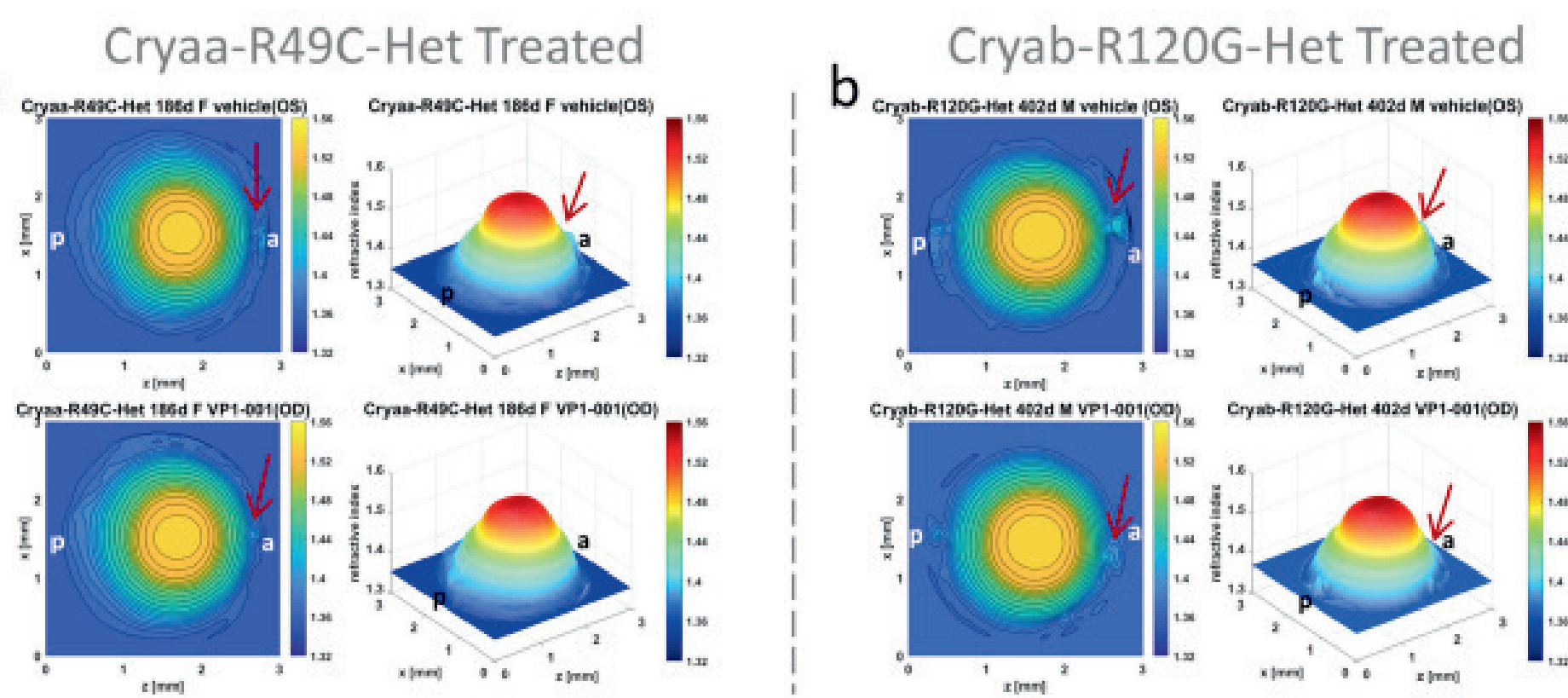


Figure 3. Refractive index profiles of two mice (a,b), with the VP1-001 treated eyes exhibiting smoother profiles and less polar disturbances compared to the vehicle-treated eyes. (Wang et al. 2022)

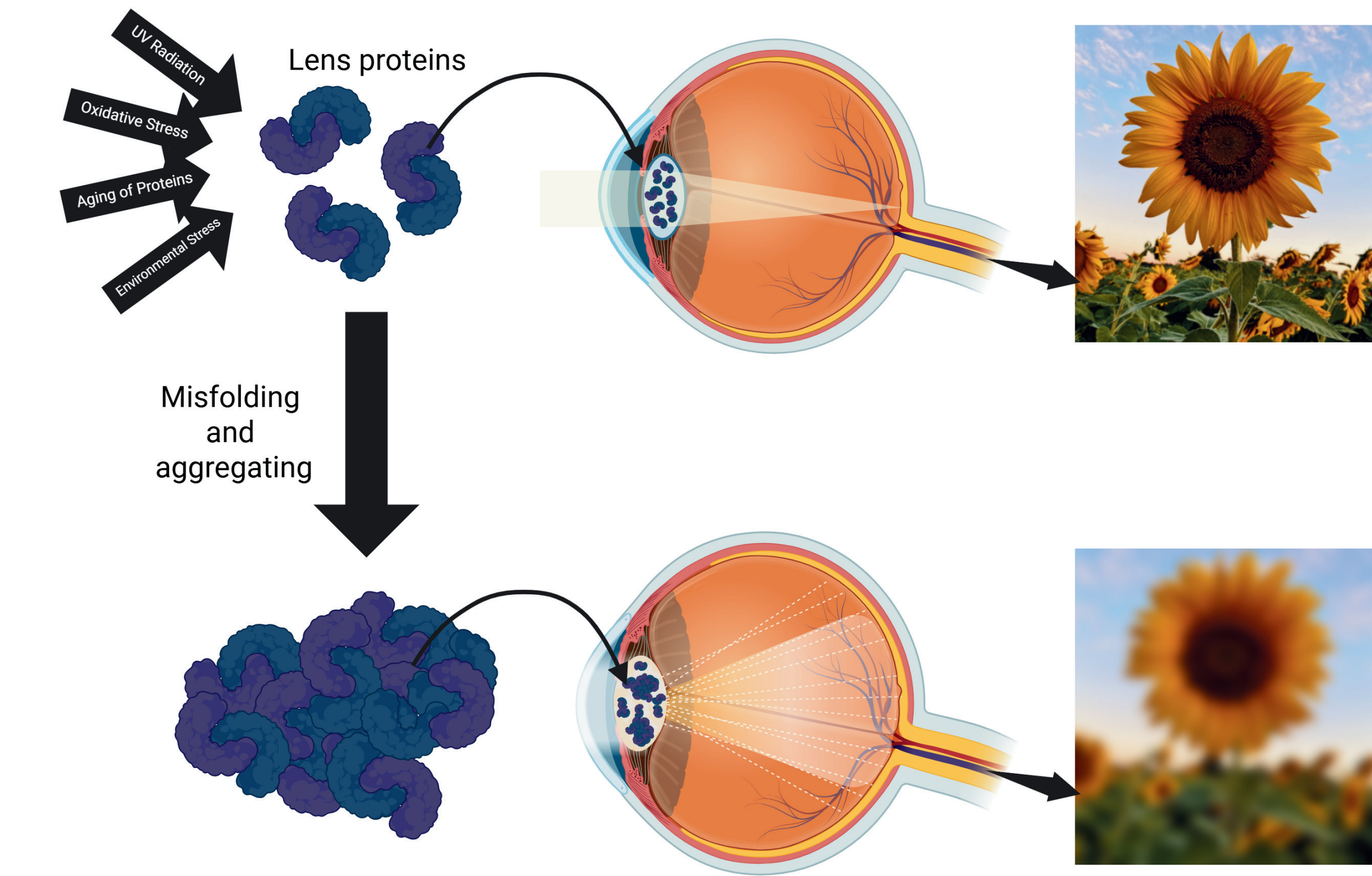


Figure 2: Due to stress, proteins in the lens can misfold and aggregate. This blocks the travel of light from focusing on the retina correctly and causes the blurry vision of cataracts. (Made in BioRender.com)

Lanosterol

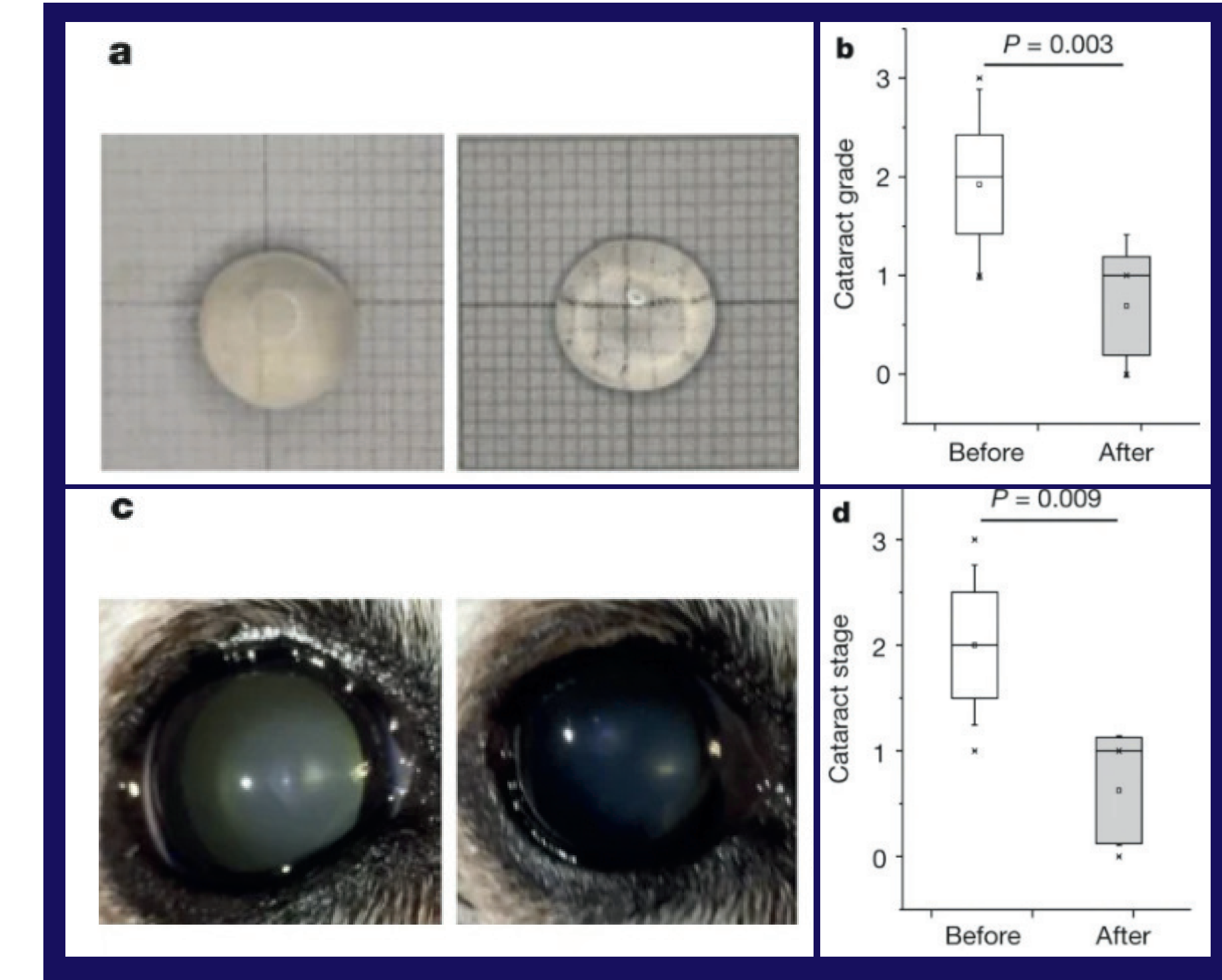


Figure 4: A. Cataractous rabbit lens before (left) and after (right) treatment, showing a clearer lens. B. A decrease in cataract grade was observed after lanosterol treatment. C. Cataractous dog lens before (left) and after (right) treatment. D. A decrease in cataract grade observed after lanosterol treatment (Zhao et al. 2015)

- Mutations in the Lanosterol Synthase (LSS) gene were found to be linked to congenital cataracts (Chen & Liu, 2017)
- Lanosterol synthase is responsible for the conversion of (S)-2,3-oxidosqualene to lanosterol (Chen & Liu, 2017)
- Found that Lanosterol binds to the hydrophobic regions of protein aggregates to make them water soluble again (Zhou et al. 2019)
- Rabbit, dog, embryonic mice, monkey models show increase in lens clarity upon lanosterol treatment (Zhao et al. 2015; Zhang et al. 2022)

Mechanism

- As a person ages, the proteins that compose the lens of the eye often begin to misfold and bundle together (Abrol et al. 2024)
- This blocks light from entering as it should, and instead scatters it, causing blurry vision (Fig. 2) (Lee and Afshari, 2017)
- Cataract surgery treats this by removing the lens and replacing it with an artificial one called an intra-ocular lens. (Abhay & Raj, 2005)
- These 4 proposed treatments seek to either remove the stress that is causing the lens proteins to denature or break up the clumps and regain solubility

N-acetylcarnosine

- N-acetylcarnosine metabolizes into L-carnosine upon entering the cornea. This is a dipeptide that can reduce oxidative stress, which often induces cataracts (Dubois and Bastawrous 2017)
- This treatment has been studied the most in humans, and much of the research seems to support its use (Babizhayev et al. 2009)
- However, there also conflicting research that suggests that long-term use may negatively impact vision. (Babizhayev & Vegerov 2016)

Fidarestat

- Fidarestat is also an Aldose Reductase Inhibitor (ARI), targeting the enzyme Aldose Reductase from reducing glucose to sorbitol (Srivastava et al. 2011)
- Rats with diabetic cataracts showed a lower formation of cataracts when treated with fidarestat compared to those given control treatment (Drel et al. 2008)

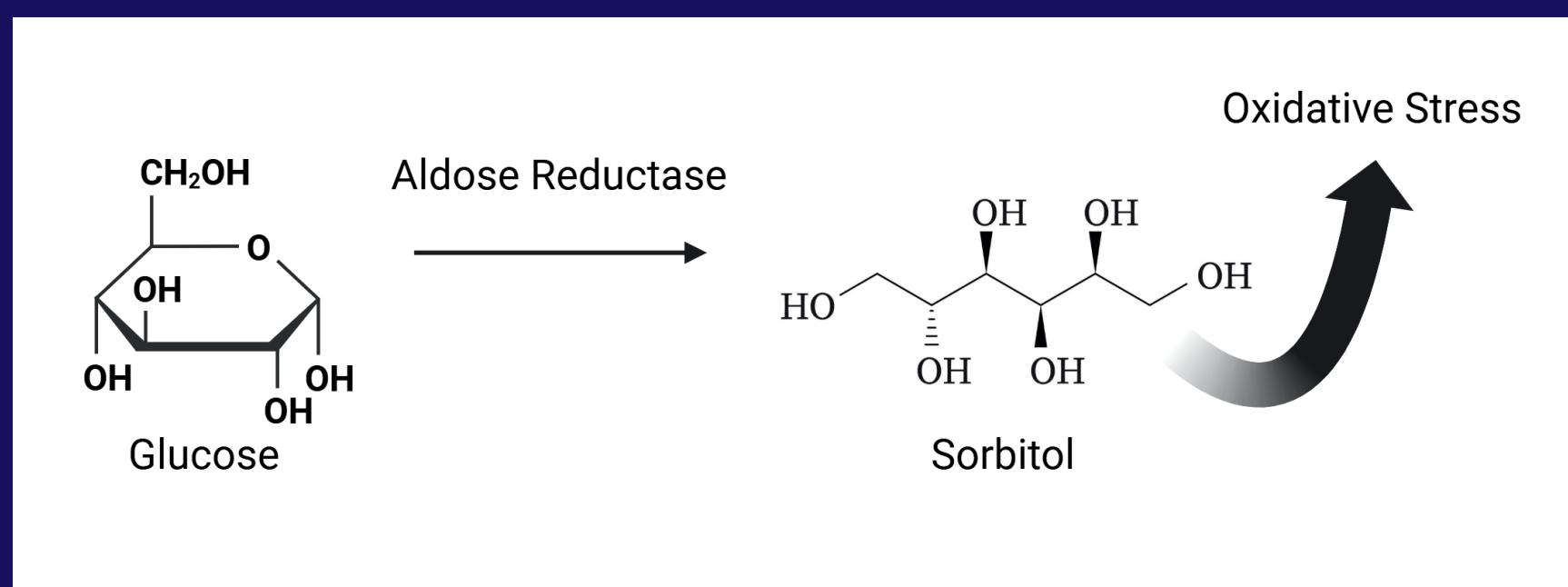


Figure 5: The enzyme Aldose Reductase reduces glucose to sorbitol, increasing the latter's concentration which can cause oxidative stress (Made in BioRender.com)

Future Research

Table 1. Mechanisms and Limitations of Proposed Treatments

Treatment	Mechanism	Key Limitation
Oxysterol VP1-001	Binds and stabilizes α -crystallins to stop misfolding and restores their chaperone activity	No human trials
Lanosterol	Binds protein aggregates to dissolve them, restoring solubility	Some conflicting studies, needs more evidence in human trials
N-acetylcarnosine	Reduces oxidative stress in lens	Possible long-term adverse effects, decreasing interest in research
Fidarestat	Reduces sorbitol accumulation, decreasing oxidative stress	No human trials

- All 4 proposed treatments have the advantage of being administered as eye drops, among other routes, which makes them more accessible than surgery.
- N-acetylcarnosine has had the longest time being researched, but interest in it has waned.
- Oxysterol VP1-001 and Fidarestat have promising results but require further testing in humans
- Lanosterol may have the most promising position in current research, with many animal models. Further studies should focus on testing in humans in the hope that it can be used as a non-surgical treatment

Acknowledgements

I would like to express deep gratitude towards my capstone mentor Dr. E.C. Cline for guiding me through this literature review with patience and diligence. I thank Dr. Jutta Heller for helping to consolidate this work to present. I am also grateful for my professors who have instilled the knowledge and curiosity that moved me towards this project, and to the University of Washington Tacoma for the resources it provided which helped me to complete this project.

References

