THE ROLE OF RESVERATROL ON TGF BETA AND MMP-2 EXPRESSION IN ANIMAL MODELS OF FORM DEPRIVATION MYOPIA: LITERATURE REVIEW

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KEYWORDS

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ABSTRACT:

The immune system causes inflammation to draw prostaglandins, cytokines, blood cells, and cytotoxic factors, also growth factors to the infection or injury. Like myopia, this response causes local metabolic changes and tissue remodelling. TGF-β and MMP-2 increase whereas collagen (COL)1 decreases in myopic eyes. This suggests that inflammation may cause myopia. In induced myopia, topical resveratrol (RSV) boosts RPE layer effectiveness through NF-κB signalling transduction, resulting in anti-inflammatory effects and MMP-2 and TGF-β inhibition. Many medication administration strategies have been examined, including subconjunctival injection, which penetrates the posterior sclera and deposits the active material in the RPE. Few studies have examined the effects of subconjunctival resveratrol injection on MMP-2 and TGF-β in animal models of form deprivation myopia (FDM). To better understand resveratrol as anti-inflammatory in scleral remodelling, researchers will study the impact of resveratrol on MMP-2 and TGF-β expression in rabbits with form-deprivation-induced myopia.

1. Introduction

Myopia, or near-sightedness, is the predominant refractive condition among children and adolescents. Myopia can impair vision, marked by the blurriness of distant objects. This syndrome typically arises from aberrant elongation of the eyeball, resulting in the distorted picture produced by the cornea and lens falling anterior to the retinal photoreceptors[1]. Myopia is among the most prevalent ocular disorders globally, affecting 10–30% of the adult population in numerous nations and 80–90% of young adults in certain areas of East and Southeast Asia. Pathological myopia, a severe form of myopia, may be linked to other ocular conditions. Myopia is classified based on severity, anatomical features, genetic influences, age of onset, rate of advancement, presence of clinical disorders, and theories regarding its origin. According to the severity, myopia can be classified as low (<3.00 D), moderate (between 3.00 D and 5.00 D), or high (>5.00 D) (Figure 1). The axial length of a typical adult is 24mm; measurements beyond this threshold indicate myopia, while values surpassing 26-27mm are classified as extreme myopia. The correlation between axial length and refractive error may be non-linear and subject to variation based on age, ocular dimensions, or both factors[1,2].

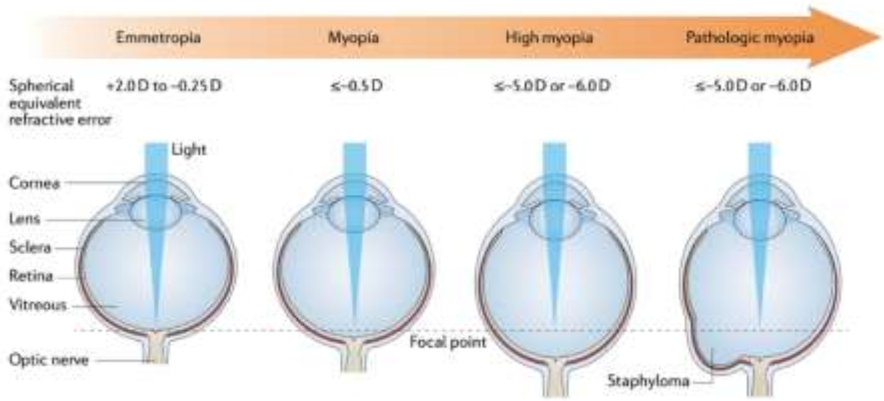

Figure 1. Alterations in ocular morphology in myopia[1]

Myopia, or nearsightedness, is a common condition that usually develops in childhood and early adulthood as a result of excessive elongation of the eyeball, forcing distant pictures to focus in front of the retina, resulting in blurred vision at a distance. Myopia arises from an extension of the axial length and a morphological alteration of the eyeball from spherical to elliptical. Scleral tissue remodelling is accelerated by an inordinate increase in axial length, which results in the thinning of the posterior pole of the sclera. Additionally, biomechanical characteristics and scleral remodelling are influenced by changes in collagen metabolism and collagen fibrils during myopization and emmetropization[1]. Figure 2 illustrates that the sclera is a tissue target and collagen is a protein target, as Yang et al. assert that scleral collagen expression and scleral remodelling are critical components in the biological process of myopia. An increase in the severity of myopia may elevate the risk of changes in ocular tissue, especially in instances of high-degree and pathological myopia[3]. This may lead to vision impairment or irreversible blindness, including sight-threatening disorders such as glaucoma and macular hole also retinal detachment [1].

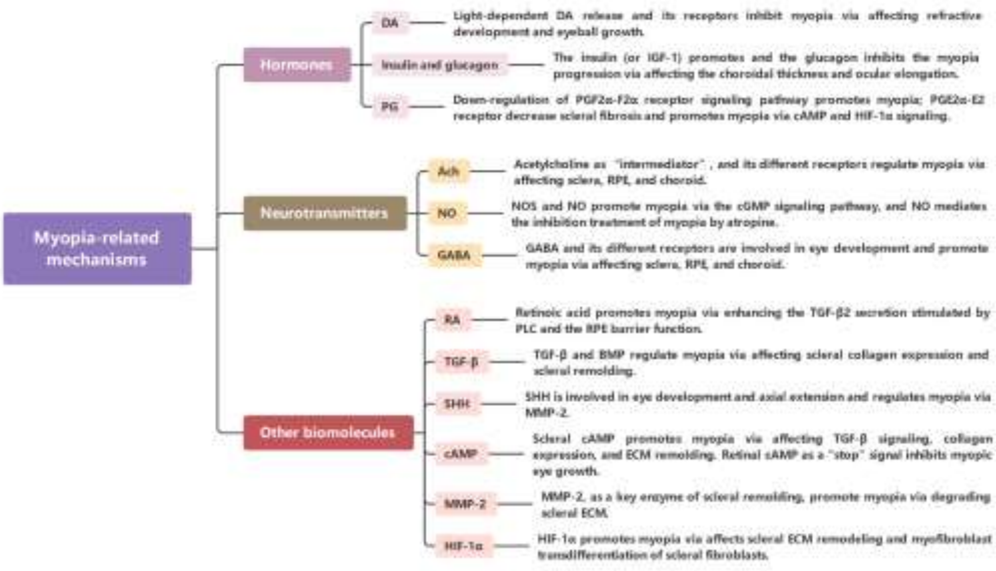

Figure 2. An overview of the pathways and signalling systems related to myopia[3]

Inflammation

Inflammation involves a series of cellular and molecular processes that facilitate the repair of minor injuries and promote tissue regeneration. In the event of procedural failure, inflammation may intensify and lead to disease progression. Injuries or alterations resulting from trauma, non-communicable diseases, infection, stress, even autoimmune disorders typically elicit a response characterized by augmented blood flow to the impacted region, an elevation in the quantity of white blood cells within the affected tissue, and enhanced phagocytic activity to eradicate the causative agent, subsequently succeeded by a reduction in these mechanisms to facilitate healing[4].

Immune System

The immune system's main goal is to eliminate viruses, bacteria, parasites, fungi, and compromised cells. The immune system has innate and adaptive components. Despite their different responsibilities in protecting the body, both work together to eliminate harmful antigens. The basic defense mechanism, the innate immune system, initiates inflammation. The adaptive immune system is more advanced and may "learn" and "memory" antigens over time. Both branches search the organism for antigens, but activating them requires different ways. Lymphocytes are produced and differentiated in the bone marrow and thymus. T lymphocytes undergo differentiation in the thymus, where they experience positive and negative selection, activating solely upon recognition of MHC markers that present antigens. Lymph nodes and the spleen serve as reservoirs for inactive immune cells. The lymphatic system is purified by lymph nodes, which also help B and T cells and antigen-activated leukocytes communicate. Inactive leukocytes monitor blood and tissues for foreign antigens and are triggered by cytokines at areas of inflammation. Leukocytes eliminate foreign antigens, infected cells, injuries, and necrotic cells to facilitate healing. Cytokines function as paracrine, autocrine, or endocrine messengers, engaging with immune cells and various biological systems to produce antagonistic, synergistic or intricate effects. The environment of cytokine influences adaptive immune response. The synthesis of IFNγ and IL-2 is essential for the activation of cytotoxic T cells and the response to bacterial and viral infections. High IL-6 and IL-4 levels activate and multiply B cells, enhancing antibody synthesis[4].

Cellular defenses as well as chemical and physical barriers are components of the innate immune system. In addition to the skin, there are physical barriers that include the respiratory and digestive tract mucous membranes. The stomach's acidic pH functions as a chemical barrier. The simpler innate immune system elicits a fast, nonspecific inflammatory response, resulting in warmth, redness, pain, and swelling in skin injuries. Pattern recognition receptors (PRRs) of the innate immune system identify bacterial membrane ligands to detect various microbial antigens and trigger an inflammatory response. The circulation include soluble pattern recognition receptors, including components of the complement system. The complement system attracts inflammatory cells by disrupting bacterial membranes using proteins. The innate immune response encompasses neutrophils, macrophages, dendritic cells, and natural killer cells. Dendritic cells, neutrophils, and macrophages phagocytize antigens and microorganisms, generating reactive oxygen species to eliminate bacteria. Natural killer cells eliminate virus-infected cells. Upon activation, NK cells recruit immune cells through the secretion of cytokines. Activated macrophages also dendritic cells serve as antigen-presenting cells (APC) that enhance the adaptive immune response within the lymph nodes. The innate immune system relies on cytokines such as IL-1, IL-6, TNF-α, and IFN-α. Immunological mediators activate the hypothalamic-pituitary-adrenal (HPA) axis, it cause sickness behaviour, including fever, pain, and tiredness. In addition, insulin, cholesterol, and lipoproteins have been shown to play important functions in the innate immune system[4].

The advanced adaptive immune system, unique to vertebrates, improves antigen elimination and establishes memory to speed up antigen clearance after exposure. Adaptive responses to primary antigens take 10-14 days in humans. Both helper T cells (TH) (CD4+) and cytotoxic T cells (TC) (CD8+) travel via the circulation and lymphatic system and reside in secondary lymphoid organs. After antigen presentation by APCs, T cells become memory and effector cells. Effective T cytotoxic cells differentiate into CTL and destroy antigen-presenting cells. B cell development and cytokine generation are controlled by effector TH cells. Innate immune cells' cytokine milieu governs TH cell development, directing the immune response along one of two paths. The cytokines TNF-α, IFN-γ, also IL-2 released by TH1 cells activate cytotoxic T lymphocytes and boost cellular immunity. Fighting intracellular bacteria and viruses requires cellular immunity. Instead, TH2 cells release IL-4 and IL-5 to activate and differentiate B cells, boosting humoral immunity. Memory TC, TH cells monitor the circulation and lymphatic system for antigen exposure. A quick and successful secondary response to antigens requires both cell types. TH17 and regulatory T cells (TREG) also play a major role in the immune response. TREG cells control immune responses by secreting IL-10 and TGF-β, reducing TH1 and TH2 cell overactivation and avoiding autoimmune or allergic problems. TH17 cells release IL-17 and attract neutrophils, especially in mucosal membranes, to fight infections like Candida. Both primary and secondary antigen contacts trigger an antibody response in the humoral immune response, which fights extracellular germs. Lymph nodes house most immature B lymphocytes. When B cells are activated, effector plasma cells are produced. These cells produce antibodies that are specific to the antigen, which either neutralize free antigens or tag infected cells for destruction. Memory B cells exhibit prolonged lifespan and generate bigger targets for lytic or phagocytic immune cells upon subsequent encounters.. Macrophages and natural killer cells that recognize antibody complexes phagocytose neutralized antigens or infected cells. Antibodies can activate or prolong complement cascades[4].

The ocular immune system

TGF Beta and MMP-2 in ocular tissues

In ocular tissues, TGF-β is a crucial growth factor that governs cellular activity. Through development, tissue repair, and numerous normal or pathological processes, this regulates cellular migration, proliferation, apoptosis, and protein synthesis. The TGF-β protein promotes extracellular matrix production and limits cell proliferation. Furthermore, TGF-β leads to the creation of many growth factors, such as CTGF, PDGF, FGFs, VEGF, and TGF-β 1. All of these factors affect tissue repair after injury. Three TGF beta isoforms—TGF-β 1, β2, and β3—in mammalian tissues exhibit similar reactions in vitro but have varying activities and manifestations in vivo. Gene knockout mice show individual isoform functions in embryonic development and tissue morphogenesis. In fibrotic diseases related to wound healing in ocular tissues, excessive TGF β activation, like in other tissues, impairs vision and disrupts tissue equilibrium. A current literature review on TGF β and its signalling pathways in ocular disease etiology is presented here. Targeting the TGF-β signalling system can be used to treat many illnesses. In vivo and in vitro, TGF-β increases collagen-related gene expression in ocular mesenchymal cells. A recent study used gene expression arrays from embryonic fibroblasts from embryos lacking Smad2 or Smad3 to compare Smad2 and Smad3. Regulated by Smad2, alpha-smooth muscle actin (αSMA) expression is essential for fibroblast transition into myofibroblasts. Smad3 regulates Snail, the main transcription factor involved in epithelial-mesenchymal transition (EMT), which underlies eye tissue fibrosis. Matrix metalloproteinase-2 is dependent on Smad2, although most extracellular matrix components and enzymes involved in matrix reorganization and maturation are dependent on Smad3. Repairing skin tissue using Smad3-deficient mice is faster and less fibrotic. In transgenic mice, dominant-negative expression of the TGF-β type II receptor in collagen I-expressing fibroblasts causes systemic tissue fibrosis due to unregulated Smad signalling pathway activation. The central linker region of Smad3 is phosphorylated by various MAPKs, which may help Smad translocate to the nucleus and promote fibrosis-related gene expression[5].

Zinc-dependent endopeptidases, known as MMPs, are frequently secreted as pro-enzymes that are activated in the extracellular milieu. However, there are also certain membrane-bound variations of MMPs. MMP family members are further distinguished by their evolutionary relationship to vertebrate collagenases, their need for zinc at the active site, and their vulnerability to inhibition by endogenous tissue inhibitors of metalloproteinases (TIMPs). MMPs exhibit several shared structural characteristics, notably a propeptide at the N-terminal that hinders the catalytic domain of the protein by binding to the zinc atom present within it. This propeptide undergoes proteolytic cleavage, which results in enzyme activation. The substrate specificity is primarily determined by the configuration of the enzyme's catalytic subunits, the hemopexin domain at the C-terminal, and various small domains unique to specific family members. The small domains and their resulting variations have produced a set of enzymes that are unique in both evolutionary and functional dimensions, exhibiting distinct but overlapping substrates. The regulation of MMP primarily occurs at the transcriptional level (Figure 3)[6,7].

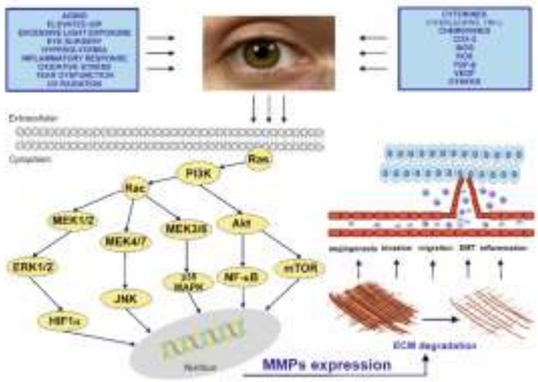

Figure 3. Diagram illustrating the molecular mechanisms that initiate MMP expression and the consequent effects in ocular disorders[8].

MMP is typically synthesized only when necessary. A variety of growth factors and cytokines, such as tumor necrosis factor-alpha (TNF-alpha), interleukin-1 (IL-1), and transforming growth factor-beta (TGF-β), have the potential to either stimulate or suppress MMP production. The expression of MMP is stimulated by changes in cell morphology and interactions with the extracellular matrix (ECM). Additional regulation is affected by proteins typically associated with inflammation and stress, including SP-1, the Ets family, and NF-kB. The extracellular matrix (ECM) structure of tissues consists of cells that are arranged within it. This framework consists of a varied and tissue-specific combination of fibrous proteins (mostly collagen), glycosaminoglycans, and proteoglycans. In order to preserve cellular and tissue homeostasis, the extracellular matrix (ECM) functions as a dynamic framework that undergoes continuous remodeling. The remodeling process is primarily facilitated by a diverse group of zinc-dependent proteolytic enzymes called MMPs, which act on substrates such as cell adhesion molecules (e.g., e-cadherin), secreted cytokines (e.g., transforming growth factor-beta, tumor necrosis factor-alpha), and extracellular matrix components (e.g., collagen, fibronectin). Growth, development, morphogenesis, tissue healing, and remodeling all depend on matrix metalloproteinases (MMPs) breaking down extracellular matrix (ECM). Figure 4 demonstrates that more than fifty percent of the MMP family members facilitate bone development also formation under normal physiological settings. Moreover, mutations in the MMP14 as well as MMP2 genes in humans have been associated with uncommon bone diseases characterized by bone tissue degradation and diminished height[7].

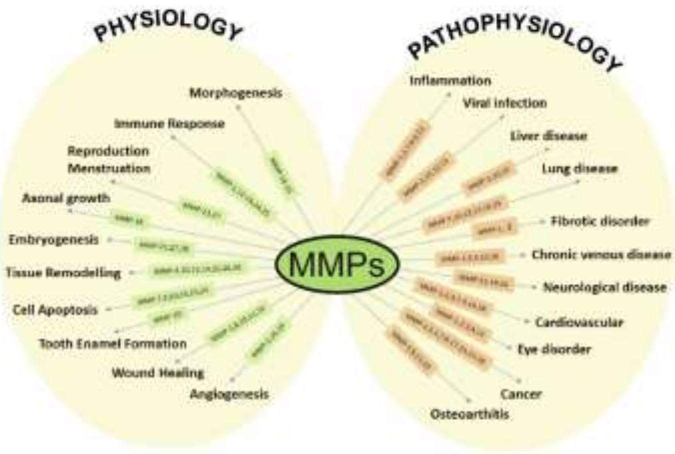

Figure 4. MMP-regulated physiological and pathological processes[8]

The reversible inhibition of matrix metalloproteinases (MMPs) through 1:1 binding has been made possible by the identification of four homologous TIMPs (TIMP-1, -2, -3, and -4). The progression of ECM remodeling is frequently dictated by the ratio of MMPs to TIMPs, with each TIMP capable of inhibiting several MMPs exhibiting varying specificity and affinity. Changes in MMP expression and activity are a common occurrence in normal biological processes, such as wound healing. However, an imbalance between MMPs and TIMPs can result in abnormal tissue remodeling as a result of the excessive degradation or accumulation of ECM components, as well as changes in growth factors, receptor signaling, and cellular migration. Diseases affecting the cardiovascular system (like atherosclerosis), the musculoskeletal system (like arthritis), the neurological system (like Alzheimer's and Parkinson's), and cancer are among the pathological disorders that can arise from these abnormalities[7,8].

Form Deprivation Myopia

Form Deprivation Myopia (FDM) and Lens generated Myopia (LIM) are experimental myopias generated by changing animals' visual experience. Lens-induced myopia alters the animal's vision, while form deprivation myopia obscures it. Rabbits, chickens, mice, primates, and tree shrews have been tested using this method[9]. Full D2R agonists regulate ocular growth and refraction and partially suppress form deprivation myopia (FDM) via D2R activation under low dopamine levels. Decreased D2R-mediated signaling correlates to myopia development, they found. A chick study in LIM found that hyperopic defocus reduced dopamine levels[10]. FDM and LIM may have different dopaminergic system functions due to the retina's sensitivity to different optical approaches for myopic development. FDM uses an open-loop system to accelerate ocular growth in the absence of form vision, provided the diffuser remains in place and developmental plasticity continues[11]. LIM is a closed-loop system that maintains ocular elongation until the applied defocus compensation threshold is reached. Eye deprivation can be performed by suturing both eyelids, applying a diffuser, tattooing the cornea, or placing contact lenses on the scleral-corneal cup for a set time[9]. In their myopia investigation, Abdullah et al. examined form deprivation. Lens-induced and form-deprivation myopia are common myopia inducers. The FDM approach creates an open system without an endpoint (light points are sensed by the RPE), while lens-induced myopia creates a closed system that reduces lens-induced hyperopic defocus. Both reduce dopamine release, which may slow scleral eye elongation[12,13].

Resveratrol

Resveratrol (3,5,4'-trihydroxy-trans-stilbene) is a natural phenol and phytoalexin that is formed by a diverse array of plants in response to pathogen infestations or injury, including those caused by bacteria and fungi. Resveratrol (RSV) is found in the skins of grapes, as well as in blueberries, raspberries, and mulberries. The "French Paradox," which highlights the cardiovascular health advantages of red wine containing non-flavonoid resveratrol, generated significant interest in the compound. Notwithstanding a diet rich in saturated fats, the French population exhibits low incidence of cardiovascular events. Subsequent research indicates that resveratrol possesses antioxidant, anti-inflammatory, cardioprotective, neuroprotective, chemotherapeutic, and anti-aging activities.

Resveratrol's health impacts include many mechanisms. Resveratrol can boost the expression of numerous antioxidant enzymes, assessing their impact on reducing oxidative stress. Resveratrol stimulates sirtuin (SIRT)1, which regulates metabolism, stress tolerance, cell survival, aging, inflammatory immunology, endothelial function, and circadian rhythms[14]. Resveratrol activates SIRT1, making it beneficial for metabolic, inflammatory, and cell cycle disorders. Numerous in vivo and in vitro studies show resveratrol's anti-inflammatory properties[15]. A study found that resveratrol inhibits spleen cell proliferation stimulated by ConA, IL-2, or allo-antigen, as well as suppresses lymphocyte and macrophage production of IL-2, TNF-α, IFN-γ, and IL-12. Resveratrol reduces IL-6, IL-1α, and TNF-α synthesis at a dose-dependent level, as well as mRNA expression and IL-17 protein release in vitro. Polydatin, a natural precursor of resveratrol, significantly reduced the expression of TNF-α, IL-1β and IL-6 in both in vivo and in vitro settings with Mycoplasma gallisepticum, indicating anti-inflammatory properties[16].

Stilbenoids are amphiphilic, acidic polyphenols that have anti-inflammatory qualities, such as resveratrol. It inhibits COX-1 and COX-2, also COX transcription factor activity, affecting several specific targets, including COX, 5-LOX, and protein kinase B. Multiple studies demonstrate that resveratrol suppresses the release and expression of inflammatory factors. In rabbit models, resveratrol inhibits the production of reactive oxygen species, caspase-3/9, macrophage inflammatory protein-2, cyclooxygenase-2, and NF-κB, thereby reducing inflammation in acute pharyngitis via serum interleukin-6. In a model of acetic acid-induced pleuritis, resveratrol diminishes ear edema in mice, decreases white blood cell counts, reduces nitric oxide production, and enhances serum superoxide dismutase activity while lowering malondialdehyde levels and raising serum activity. In a model of carrageenan-induced synovitis, resveratrol lowers TP, PGE2, NO, and MDA, confirming its analgesic and anti-inflammatory properties. Resveratrol inhibits microglial activation, which releases pro-inflammatory substances, reactive oxygen species, and signaling pathways that induce neuroinflammation. Resveratrol regulates intestinal cell inflammation in in vitro studies by diminishing NF-κB activation and averting mitochondrial dysfunction at moderate to high concentrations. Resveratrol modulated anti-inflammatory miRNAs[17,18], which in turn reduced intestinal carcinogenesis, neutrophil infiltration, NF-κB activation, and TNF-α generation in in vivo tests. Salehi et al. found that resveratrol significantly reduces damage and inflammation induced by lysophosphatidylcholine, which may aid in the management of arteriosclerosis. Resveratrol reduces oxidative stress and inflammation, lowers the risk of cancer, and is being researched as an anti-inflammatory medication to improve patients' quality of life[19].

Resveratrol has antioxidant, cardioprotective, neuroprotective, anti-inflammatory, and anticancer activities[16,19]. The body quickly absorbs and metabolizes phytoalexin. Risk signs like microbial invasion or tissue injury trigger inflammation[16]. Myopia patients may benefit from resveratrol (RSV) supplementation. Multiple factors, such as TGF-β, MMP2, and collagen I, have been linked to myopia development. The scleral extracellular matrix (ECM) is remodeled and collagen formation is reduced by TGF-β, which is present in ocular tissues. Nuclear factor-κB activation intensifies collagen disruption by increasing MMP2 synthesis and decreasing tissue inhibitor activity[20]. Hsu et al. found that RSV-treated hamsters had shorter ocular lengths. Eyes treated with RSV showed decreased ocular tissue remodeling, myopia, and inflammatory cytokines (TGF-β, NFκB, TNFα, MMP2, IL-1β, and IL-6). Collagen I expression increased in RSV-treated eyes. This suggests that resveratrol may regulate like atropine[20,21].

2. Conclusion

Resveratrol as an anti-inflammatory agent may suppress MFD-induced myopia in animal models, while RPE cells exhibit alterations in TGF-β and MMP-2 expressions, which function as remodeling agents. Consequently, resveratrol may aid in the management of various inflammatory illnesses, including myopia.

References

1. Baird, P. N., S.-M. Saw, C. Lanca, J. A. Guggenheim, E. L. Smith Iii, X. Zhou, K.-O. Matsui, P.-C. Wu, P. Sankaridurg, A. Chia, M. Rosman, E. L. Lamoureux, R. Man, and M. He. 2020. Myopia. *Nature Reviews Disease Primers*, 6(1):99, https://doi.org/10.1038/s41572-020-00231-4
2. Chamberlain, P., P. Lazon De La Jara, B. Arumugam, and M. A. Bullimore. 2021. Axial length targets for myopia control. *Ophthalmic and Physiological Optics*, 41(3):523–531, https://doi.org/10.1111/opo.12812
3. Yang, J., X. Ouyang, H. Fu, X. Hou, Y. Liu, Y. Xie, H. Yu, and G. Wang. 2022. Advances in biomedical study of the myopia-related signaling pathways and mechanisms. *Biomedicine & Pharmacotherapy*, 145:112472, https://doi.org/10.1016/j.biopha.2021.112472
4. Bennett, J. M., G. Reeves, G. E. Billman, and J. P. Sturmberg. 2018. Inflammation–Nature's Way to Efficiently Respond to All Types of Challenges: Implications for Understanding and Managing "the Epidemic" of Chronic Diseases. *Frontiers in Medicine*, 5:316, https://doi.org/10.3389/fmed.2018.00316
5. Saika, S. 2006. TGFb pathobiology in the eye. *Laboratory Investigation*
6. Sivak, J. M., and M. E. Fini. 2002. MMPs in the eye: emerging roles for matrix metalloproteinases in ocular physiology. *Progress in Retinal and Eye Research*, 21(1):1–14, https://doi.org/10.1016/S1350-9462(01)00015-5
7. Weinreb, R. N., M. R. Robinson, M. Dibas, and W. D. Stamer. 2020. Matrix Metalloproteinases and Glaucoma Treatment. *Journal of Ocular Pharmacology and Therapeutics*, 36(4):208–228, https://doi.org/10.1089/jop.2019.0146.
8. Caban, M., K. Owczarek, and U. Lewandowska. 2022. The Role of Metalloproteinases and Their Tissue Inhibitors on Ocular Diseases: Focusing on Potential Mechanisms. *International Journal of Molecular Sciences*, 23(8):4256, https://doi.org/10.3390/ijms23084256
9. Putri Rahmani, K., and L. Indriaswati. 2022. Form Deprivation Myopia (FDM) Effect in Sclera Layer of Animal Model: A Literature Review. *International Journal of Research Publications*, 116(1) https://doi.org/10.47119/IJRP1001161120234392
10. Huang, F., Q. Wang, T. Yan, J. Tang, X. Hou, Z. Shu, F. Wan, Y. Yang, J. Qu, and X. Zhou. 2020. The Role of the Dopamine D2 Receptor in Form-Deprivation Myopia in Mice: Studies With Full and Partial D2 Receptor Agonists and Knockouts. *Investigative Opthalmology & Visual Science*, 61(6):47, https://doi.org/10.1167/iovs.61.6.47.
11. Thomson, K., C. Karouta, and R. Ashby. 2020. Form-Deprivation and Lens-Induced Myopia Are Similarly Affected by Pharmacological Manipulation of the Dopaminergic System in Chicks. *Investigative Opthalmology & Visual Science*, 61(12):4, https://doi.org/10.1167/iovs.61.12.4.
12. Abdullah, M. R., Suhendro, Gatot, Deneska, Ria Sandi, Fauziah, Dyah, Notobroto, Hari Basuki, Lestari, Atina Yustisia, and Rosati, Denisa. 2021. Effect of Limbal Mesenchymal Stem Cell in Form Deprivation Myopia Animal Model. *Annals of the Romanian Society for Cell Biology*, 25(4):20001–20009.
13. Rosati, D., Suhendro, Gatot, Deneska, Ria Sandi, Fauziah, Dyah, and Abdullah, Muhammad Rizqy. 2022. The Effect of CD 90 Expression after Intrasclera Limbal Mesenchymal Stem Cell Injection in Form Deprivation Myopia Animal Mode. *International Journal of Research Publications*, 94(1):429–437.
14. Ramírez-Garza, S., E. Laveriano-Santos, M. Marhuenda-Muñoz, C. Storniolo, A. Tresserra-Rimbau, A. Vallverdú-Queralt, and R. Lamuela-Raventós. 2018. Health Effects of Resveratrol: Results from Human Intervention Trials. *Nutrients*, 10(12):1892, https://doi.org/10.3390/nu10121892
15. Berman, A. Y., R. A. Motechin, M. Y. Wiesenfeld, and M. K. Holz. 2017. The therapeutic potential of resveratrol: a review of clinical trials. *Npj Precision Oncology*, 1(1):35, https://doi.org/10.1038/s41698-017-0038-6.
16. Meng, X., J. Zhou, C.-N. Zhao, R.-Y. Gan, and H.-B. Li. 2020. Health Benefits and Molecular Mechanisms of Resveratrol: A Narrative Review. *Foods*, 9(3):340, https://doi.org/10.3390/foods9030340
17. Koushki, M., N. Amiri-Dashatan, N. Ahmadi, H. Abbaszadeh, and M. Rezaei-Tavirani. 2018. Resveratrol: A miraculous natural compound for diseases treatment. *Food Science & Nutrition*, 6(8):2473–2490, https://doi.org/10.1002/fsn3.855

18. Cheng, C. K., J. Luo, C. W. Lau, Z. Chen, X. Y. Tian, and Y. Huang. 2020. Pharmacological basis and new insights of resveratrol action in the cardiovascular system. *British Journal of Pharmacology*, 177(6):1258–1277, https://doi.org/10.1111/bph.14801
19. Salehi, B., A. P. Mishra, M. Nigam, B. Sener, M. Kilic, M. Sharifi-Rad, P. V. T. Fokou, N. Martins, and J. Sharifi-Rad. 2018. Resveratrol: A Double-Edged Sword in Health Benefits. *Biomedicines*, 6(3):91, https://doi.org/10.3390/biomedicines6030091
20. Bryl, A., M. Falkowski, K. Zorena, and M. Mrugacz. 2022. The Role of Resveratrol in Eye Diseases—A Review of the Literature. *Nutrients*, 14(14):2974, https://doi.org/10.3390/nu14142974
21. Hsu, Y.-A., C.-S. Chen, Y.-C. Wang, E.-S. Lin, C.-Y. Chang, J. J.-Y. Chen, M.-Y. Wu, H.-J. Lin, and L. Wan. 2021. Anti-Inflammatory Effects of Resveratrol on Human Retinal Pigment Cells and a Myopia Animal Model. *Current Issues in Molecular Biology*, 43(2):716–727, https://doi.org/10.3390/cimb43020052.