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Potential Role of *Shodhana* and *Rasayana* in Age-Related Macular Degeneration (ARMD): An Integrative Review of Oxidative Stress and Retinal Protection

1.Dr. Tulsi Chetan Shah, 2.Dr. Pournima Vilas Fasale

Authors

1.Dr. Tulsi Chetan Shah, PG Scholar , Department of *Shalakya Tantra* ,Hon.Shri Annasaheb Dange Ayurvedic Medical College ,Ashta,Tal-Walwa,Dist-Sangli-416301 **Email:** tulsishah1220@gmail.com

2.Dr. Pournima Vilas Fasale, M.S. *Shalakya Tantra*, Department of *Shalakya Tantra* ,Hon. Shri Annasaheb Dange Ayurvedic Medical College ,Ashta,Tal-Walwa,Dist-Sangli-416301 **Email:** pournimafasale33@gmail.com

ORCID ID: 0009-0004-9082-5993

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Abstract

Background:

Age-related macular degeneration (ARMD) is a major cause of irreversible central visual impairment in older adults. Its pathogenesis involves oxidative stress, mitochondrial dysfunction, chronic inflammation, lipid dysregulation, complement activation, retinal pigment epithelium (RPE) dysfunction, and cellular senescence. Although current treatments, particularly anti-VEGF therapy for neovascular ARMD, can reduce disease activity, effective preventive strategies targeting the upstream mechanisms of retinal degeneration remain limited.

Keywords: ARMD; *Shodhana*; *Rasayana*; oxidative stress; RPE; mitochondrial dysfunction.

Objective:

This integrative review explores the potential relevance of Ayurvedic *Shodhana* and *Rasayana*, particularly *Virechana* and *Shirovirechana*, to biological mechanisms implicated in ARMD, with emphasis on oxidative stress, metabolic homeostasis, inflammation, mitochondrial function, and RPE protection.

Methods:

Ayurvedic concepts and available biomedical literature were integrated to examine possible relationships between the proposed actions of *Shodhana–Rasayana* and established mechanisms of ARMD. Evidence from metabolic, antioxidant, inflammatory, neurovascular, and retinal research was critically interpreted, distinguishing established findings from proposed mechanisms.

Results:

Virechana may provide a systemic metabolic and inflammatory framework through its reported effects on lipid and metabolic parameters, although direct evidence in ARMD is lacking. *Shirovirechana* may have relevance through nasal olfactory and trigeminal neurovascular pathways; however, direct retinal delivery and effects on choroidal circulation remain unverified. Selected *Rasayana* interventions have demonstrated antioxidant effects, including modulation of superoxide dismutase and malondialdehyde, suggesting potential relevance to oxidative retinal injury. Potential effects on mitochondrial function, inflammatory signaling, cellular senescence, and RPE survival require further validation.

Conclusion:

Shodhana–Rasayana provides a biologically plausible translational framework for investigating ARMD but should not yet be considered an established treatment. Standardized preclinical studies and well-designed clinical trials integrating molecular, imaging, and visual outcomes are required.

Introduction

Age-Related Macular Degeneration (ARMD) stands as the leading cause of irreversible visual impairment and central blindness among the elderly population worldwide, presenting a formidable challenge to global public health. [1]As global demographics shift dramatically toward an aging population, the prevalence of this ocular disorder is projected to scale exponentially over the coming decades. Globally, approximately 196 million individuals were affected by ARMD in 2020, and this number is projected to increase to nearly 288 million by 2040.[1] In India, the prevalence ranges from 1.4% to 3.1% among individuals older than 60 years, with higher rates observed in urban populations and those with

associated systemic risk factors.[2]

Characterized by the progressive, chronic degeneration of the Retinal Pigment Epithelium (RPE), Bruch's membrane, and overlying photoreceptors, ARMD robs individuals of their independent living by destroying sharp, central vision. [3,4] Despite its massive socioeconomic and clinical burden, modern therapeutic interventions remain largely reactive rather than preventive, leaving a critical therapeutic void in safeguarding the neural retina before irreversible structural damage takes hold. [5]

At the core of ARMD's complex pathogenesis is chronic oxidative stress, which acts as the primary destructive driver of RPE cell death. The human retina is uniquely vulnerable to oxidative damage due to its exceptionally high metabolic rate, continuous exposure to high-energy light, and high concentrations of easily ox disable polyunsaturated fatty acids. [6] Over time, the inability of endogenous antioxidant systems to counter excessive Reactive Oxygen Species (ROS) leads to mitochondrial dysfunction, chronic inflammation, and the toxic accumulation of lipofuscin within RPE cells. [5] While contemporary biomedical treatments like anti-VEGF intraocular injections offer remarkable efficacy for late-stage exudative ("wet") ARMD, they are invasive, costly, and fail to target the upstream, chronic oxidative decline that fuels the much more prevalent non-exudative ("dry") form of the disease. [7]

To address this systemic and cellular breakdown, attention is increasingly turning toward comprehensive traditional paradigms, specifically the Ayurvedic *Shodhana* protocols of *Virechana*, *Shirovirechana* and *Rasayana*. Within the framework of Ayurvedic medicine, the chronic tissue decay observed in ARMD closely aligns with *Dhatukshaya* (degenerative tissue depletion) affecting *Drishti* (vision). Systemically, *Virechana* expels vitiated *Pitta* and *Rakta* toxins from the lower GI tract, purifying blood channels to decrease chronic systemic inflammation.[8] Locally, *Shirovirechana* (administered via the nasal pathway) targets the supraclavicular structures, penetrating minute cranial networks (*Srotas*) to clear localized metabolic obstruction and directly optimize the ocular microenvironment. [9] Contemporary Ayurvedic literature has further explored possible mechanisms of Nasya in relation to local absorption and neurological pathways; however, these proposed mechanisms should be regarded as hypotheses rather than established mechanisms for retinal protection. [10]

A significant knowledge gap therefore persists in translating these traditional therapeutic concepts into **verifiable molecular and cellular mechanisms relevant to retinal degeneration**. While isolated research exists for both Ayurvedic clinical protocols and Western retinal biology, an integrative synthesis bridging *Virechana* ,*Shirovirechana* and *Rasayana* mechanics directly with mitochondrial protection, ROS scavenging, and RPE cell survival is largely absent from current literature. This integrative review aims to bridge that divide by evaluating how systemic metabolic detoxification and targeted cranial bio-cleansing alter specific molecular pathways to mitigate oxidative stress. By establishing this cross-disciplinary nexus, this paper seeks to provide a coherent mechanistic rationale for incorporating traditional metabolic

therapies into modern neuroprotective strategies for the retina.

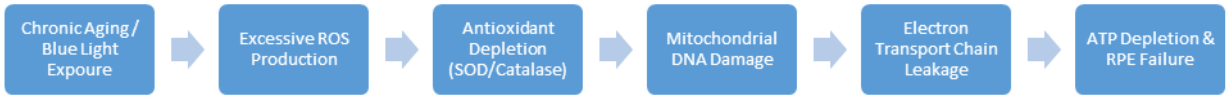
1. Pathophysiology of Oxidative Stress in the RPE

1.1 The Metabolic Vulnerability of the Neural Retina

The human retina has exceptionally high metabolic activity and oxygen consumption, making retinal cells particularly vulnerable to oxidative injury. Continuous photoreceptor outer-segment turnover, high mitochondrial activity, chronic exposure to light, and the abundance of polyunsaturated fatty acids contribute to a high oxidative burden in the outer retina and RPE. [11, 5]The RPE is positioned between the photoreceptors and choriocapillaris and is responsible for essential functions including photoreceptor outer-segment phagocytosis, visual-cycle support, nutrient transport, and maintenance of retinal homeostasis. The combination of high oxygen availability, intense metabolic activity, light exposure, and DHA-rich photoreceptor membranes makes the RPE particularly susceptible to oxidative stress. [11, 12]

1.2 Mechanics of ROS Generation and Mitochondrial Dysfunction

Under normal physiological conditions, the RPE relies on endogenous antioxidant systems—including superoxide dismutase (SOD), catalase, glutathione peroxidase, and macular pigments (lutein and zeaxanthin)—to neutralize metabolic byproducts. In Age-Related Macular Degeneration (ARMD), aging cells undergo a progressive decline in these antioxidant defenses, shifting the cellular state toward chronic oxidative stress. [5, 11]When photons interact with photosensitizers in the RPE, they trigger the formation of singlet oxygen ($^1O_2$) and superoxide anions ($O2^{\bullet-}$). This intracellular surge of Reactive Oxygen Species (ROS) primarily attacks the mitochondria. [13] Chronic ROS exposure damages mitochondrial DNA (mtDNA), leading to a defective electron transport chain that generates even greater quantities of leaking electrons. This creates a self-sustaining, destructive feedback loop of mitochondrial dysfunction, drastically reducing cellular ATP production and disabling the active transport mechanisms required to sustain photoreceptor health. [14]



1.3 Lipofuscinogenesis, Drusen Formation, and Chronic Inflammation

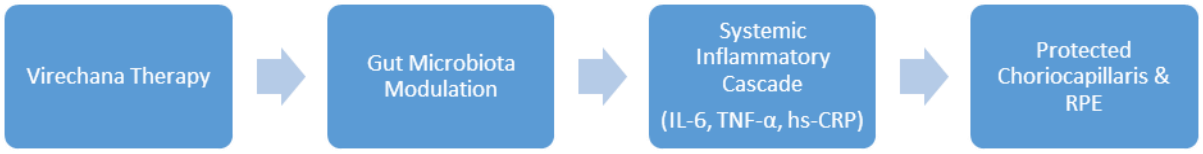
A key hallmark of the aging RPE is the incomplete lysosomal degradation of phagocytosed photoreceptor outer segments (POS), resulting in the permanent accumulation of lipofuscin within the cellular cytoplasm. A major, highly toxic component of lipofuscin is the fluorophore A2E (N-retinylidene-

N-retinylethanolamine). When exposed to blue light, A2E acts as a potent phototoxin, damaging lysosomal membranes and causing the leakage of degradative enzymes into the cytoplasm. [13]

Unable to clear this intracellular waste, the overwhelmed RPE cells extrude damaged proteins, lipids, and advanced glycation end-products (AGEs) into the extracellular space between the RPE basement membrane and Bruch's membrane. These extracellular deposits condense into clinically visible drusen. Drusen acts as a physical barrier that chokes the diffusion of vital nutrients from the choriocapillaris to the retina, inducing local hypoxia. Furthermore, these hydrophobic deposits activate the complement cascade and the NLRP3 inflammasome, recruiting macrophages and microglia.[15] This chronic, low-grade local inflammation triggers the final apoptotic pathways of RPE cells, culminating in geographic atrophy ("dry" ARMD) or driving the pathologic, VEGF-mediated neovascularization characteristic of "wet" ARMD.[12]

2. Biomedical Parameters Influenced by *Virechana*

Virechana acts primarily as a systemic metabolic resets. By clearing the gastrointestinal and hepatic pathways, it down regulates systemic vectors that otherwise damage the delicate macular microvasculature.



2.1. Inflammatory Cytokines & Biomarkers

- **Serum Interleukin-6 (IL-6) & Tumor Necrosis Factor-alpha (TNF-α)**: Clinical shifts demonstrate a statistically significant reduction in these systemic pro-inflammatory cytokines post-therapy. Lowering these circulating proteins limits the chronic, low-grade inflammatory stress (parainflammation) that triggers early drusen deposition. [16]
- **High-Sensitivity C-Reactive Protein (hs-CRP)**: Systemic levels of this acute-phase reactant drop, showing a clear reduction in vascular endothelial stress. This helps maintain the stability of the blood-retina barrier (BRB). [16]
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2.2. Lipid Profiles & Metabolic Waste Parameters

- **Serum Triglycerides & Total Cholesterol**: *Virechana* drives a documented reduction of up to 22.45% in serum triglycerides and lowers total serum cholesterol. In the context of the retina, reducing

circulating lipids limits the accumulation of oxidized low-density lipoproteins (ox-LDLs) within Bruch's membrane, directly suppressing Lipofuscinogenesis in RPE cells. [16]

- **Fasting Blood Glucose & Insulin Sensitivity**: Studies show a post-procedural decrease of up to 14.95% in fasting blood glucose along with enhanced skeletal muscle insulin receptor sensitivity. This suppresses advanced glycation end-products (AGEs), preventing matrix cross-linking in the basement membrane of the macula. [16]

2.3. Gut Microbiota Metrics (The Gut-Retina Axis)

- **Phylum-Level Shifts**: Genomically monitored via ERIC-PCR, *Virechana* suppresses pathogenic *Escherichia coli* colonization while enriching beneficial short-chain fatty acid (SCFA)-producing bacterial phyla. SCFAs travel systemically to preserve tight-junction proteins (such as Claudin-5 and Zonula Occludens-1) within the retinal vasculature. [16]

3. Biomedical Parameters Influenced by *Shirovirechana*

Shirovirechana bypasses the digestive tract entirely. It relies on lipophilic absorption through the olfactory and trigeminal nerve pathways to exert direct local action on cranial and ocular networks. The nasal cavity receives sensory innervation from the ophthalmic (V1) and maxillary (V2) divisions of the trigeminal nerve. The nasociliary nerve, a branch of V1, gives rise to the anterior ethmoidal nerve, which supplies sensory innervation to the anterosuperior nasal cavity and nasal septal mucosa. [17] The ophthalmic and maxillary divisions of the trigeminal nerve provide anatomical connections between the nasal passages and the central nervous system, supporting the possibility that nasal stimulation may influence trigeminal sensory pathways. [18]

The nasociliary nerve also gives rise to the long ciliary nerves, which carry sensory fibers from ocular structures and sympathetic fibers to the eye. Thus, the anatomical relationship between nasal trigeminal afferents, the nasociliary nerve and ocular sensory pathways provides a possible basis for investigating neurovascular effects of nasal therapies. [19]

In ARMD, oxidative stress, chronic inflammation, complement dysregulation, retinal pigment epithelial dysfunction and alterations involving the choroid are important components of disease pathogenesis.[20] Oxidative stress can promote complement activation and inflammatory responses in the RPE and outer retina, while complement-mediated processes contribute to retinal and choriocapillaris injury.[21] Therefore, trigeminal–autonomic and neurovascular modulation following nasal stimulation may be considered a hypothetical pathway through which *Shirovirechana* could influence ocular homeostasis in ARMD. However, direct clinical or experimental evidence demonstrating that *Shirovirechana* specifically modulates the nasociliary nerve or improves ARMD through this pathway is currently insufficient; this mechanism should consequently be described as proposed or theoretical rather than

established.

4. Biomedical Parameters Influenced by *Rasayana*

Rasayana therapy represents the rejuvenative component of Ayurveda and may complement *Shodhana* by supporting tissue resilience, antioxidant capacity, cellular repair, and healthy ageing. From a biomedical perspective, the potential relevance of *Rasayana* to ARMD lies primarily in modulation of oxidative stress, inflammation, mitochondrial function, and age-associated cellular damage. Experimental and human studies of selected *Rasayana* drugs have demonstrated effects on antioxidant and oxidative-stress biomarkers; however, these findings should not be interpreted as proof of efficacy in ARMD until validated in retinal and clinical studies. [22, 23]

- **Antioxidant defense:** *Rasayana* drugs may enhance endogenous antioxidant defense. A human study evaluating selected *Rasayana* drugs, including *Withania somnifera* and *Tinospora cordifolia*, reported an increase in superoxide dismutase (SOD) and a reduction in malondialdehyde (MDA), supporting their potential antioxidant activity. Endogenous antioxidant systems include SOD, catalase, glutathione-related enzymes and other antioxidant molecules. [23]
- **Lipid peroxidation:** Reduction in MDA, a commonly used marker of lipid peroxidation, may indicate reduced oxidative damage to cellular membranes. This is particularly relevant to ARMD because the RPE and photoreceptors are highly susceptible to oxidative injury, while accumulation of lipid peroxidation products can contribute to RPE dysfunction and inflammatory signaling. [23]
- **Mitochondrial protection:** By potentially reducing oxidative stress, *Rasayana* may theoretically support mitochondrial homeostasis. This is relevant to ARMD because oxidative stress-associated mtDNA damage, mitochondrial dysfunction, impaired ATP production and increased ROS generation have been implicated in RPE degeneration. However, direct evidence that *Rasayana* therapy preserves mitochondrial membrane potential or mtDNA integrity in ARMD is currently lacking and should therefore be regarded as a proposed mechanism. [24]
- **Anti-inflammatory effects:** Modulation of inflammatory pathways such as NF-κB, TNF-α, IL-6, IL-1β and NLRP3 inflammasome may theoretically be relevant to retinal ageing and ARMD. NLRP3 inflammasome activation has been demonstrated in RPE cells and is associated with production of inflammatory cytokines, particularly IL-1β and IL-18. Oxidative stress can also activate NF-κB and NLRP3-associated inflammatory signaling. [25]
- **Cellular ageing and repair:** Oxidative stress and mitochondrial dysfunction are associated with cellular senescence and impaired cellular maintenance in the ageing RPE. Pathways involving oxidative-stress responses, mitochondrial quality control, autophagy and cellular senescence are increasingly recognized in AMD biology. *Rasayana* may potentially influence cellular ageing and

repair-related pathways; however, the specific effects on DNA damage, p53/p21 signaling and cellular senescence in ARMD remain to be experimentally validated.[24]

- **Photoreceptor/RPE protection:** The RPE is essential for maintaining photoreceptor function, and oxidative stress, mitochondrial dysfunction and inflammatory processes can contribute to RPE degeneration and subsequent photoreceptor impairment in AMD. Consequently, an intervention that enhances antioxidant defense and reduces oxidative injury could theoretically support RPE survival and photoreceptor preservation. However, direct evidence for a protective effect of *Rasayana* therapy on human retinal cells in ARMD is not yet established. [24]

5. Mechanistic Synergy of *Shodhana* and *Rasayana* in Metabolic Homeostasis and Retinal Protection

5.1 The Dual-Action Model

The integration of *Shodhana* and *Rasayana* in the Ayurvedic management framework of Age-Related Macular Degeneration (ARMD) can be conceptualized as a **systemic–local–cellular model**. Within the Ayurvedic framework, visual dysfunction (*Drishti vikara*) is not considered entirely independent of systemic disturbances involving *Agni*, *Dosha* and *Dushya*. From a contemporary biomedical perspective, this systemic–local relationship is biologically plausible because AMD is a multifactorial disorder involving oxidative stress, chronic inflammation, altered lipid metabolism, mitochondrial dysfunction, RPE impairment and complement-mediated inflammatory mechanisms. Accordingly, *Virechana* may be considered a **systemic metabolic intervention**, whereas *Shirovirechana* may be explored as a **nasal neurovascular intervention**. *Rasayana* may subsequently provide a cellular-protective component through antioxidant, anti-inflammatory and cytoprotective mechanisms. Importantly, this represents a **proposed integrative model** rather than evidence that these procedures directly prevent or reverse AMD.

This interpretation is consistent with emerging evidence that ARMD is influenced by interactions among systemic metabolic factors, inflammation, lipid homeostasis, oxidative stress and the gut–retina axis.

5.2 *Virechana* and the Systemic Metabolic–Inflammatory Environment

The proposed role of *Virechana* in ARMD should be understood primarily as a **systemic metabolic hypothesis** rather than as direct retinal detoxification. Contemporary research increasingly recognizes a gut–retina axis in which intestinal microbiota, microbial metabolites, systemic immune signaling and inflammatory pathways may influence retinal homeostasis and AMD susceptibility. Dysbiosis has been

associated with altered inflammatory signaling, complement activation and changes in metabolites such as short-chain fatty acids and bile acids.

5.2.1 Lipid metabolism

Altered lipid homeostasis is an important component of ARMD pathobiology. Cholesterol, phospholipids and other lipids accumulate with age in Bruch's membrane, while drusen and basal deposits contain substantial lipid components.Clinical evidence from Ayurveda suggests that *Virechana Karma* may influence systemic lipid parameters. In a controlled clinical study involving patients with dyslipidemia, *Virechana* was associated particularly with a reduction in serum triglycerides, although the study was conducted for dyslipidemia rather than ARMD. [16]However, it cannot currently be concluded that *Virechana* reduces oxidized LDL delivery to the retina or directly prevents lipofuscin formation in RPE cells.

5.2.2 Systemic inflammation

Low-grade chronic inflammation and immune dysregulation are recognized components of ARMD pathogenesis. The gut–retina axis may contribute to this process through microbial metabolites, intestinal barrier dysfunction, systemic immune activation and inflammatory cytokines including IL-6, IL-1β and TNF-α. [16]Although Ayurvedic clinical literature has investigated inflammatory and metabolic changes following Panchakarma procedures, direct evidence demonstrating that *Virechana* specifically lowers IL-6, TNF-α or hs-CRP in patients with ARMD is presently insufficient. Consequently, these biomarkers should be regarded as **potential outcome measures for future clinical studies**, rather than established effects of *Virechana* in ARMD.

5.2.3 Glucose metabolism and advanced glycation

Hyperglycemia and advanced glycation end-products (AGEs) are relevant to ageing-related tissue injury. AGEs accumulate in Bruch's membrane and basal deposits and may alter extracellular matrix properties and RPE biology. [16]Some Ayurvedic clinical reports have described improvements in glucose and metabolic parameters following *Virechana*-based interventions; however, these findings are not sufficient to establish improved insulin sensitivity or reduced AGE formation as a specific mechanism of *Virechana* in ARMD.

5.3 *Shirovirechana* and the Nasal Trigeminal–Neurovascular Pathway

Shirovirechana, when interpreted in biomedical terms, requires particular caution. Nasal administration provides access to a highly vascularized mucosa and to sensory pathways involving the olfactory and trigeminal nerves. Experimental and pharmacological literature demonstrates that intranasally administered substances can reach the central nervous system through olfactory and trigeminal pathways

and can partly avoid gastrointestinal degradation and hepatic first-pass metabolism. [9]The nasal cavity is therefore a biologically relevant route for **nose-to-brain and neurovascular signaling**. However, this does not establish that Ayurvedic *Shirovirechana* delivers therapeutic concentrations of its constituents directly to the retina or RPE.

5.3.1 Trigeminal and nasociliary relevance

The ophthalmic division of the trigeminal nerve contributes sensory innervation to the nasal cavity and orbit, while the nasociliary nerve gives rise to the long ciliary nerves supplying sensory innervation to ocular structures. Thus, nasal stimulation has a plausible anatomical relationship with trigeminal and ocular sensory pathways. Intranasal drug-delivery studies demonstrate that the olfactory and trigeminal pathways can provide routes for neural communication between the nasal mucosa and CNS.

5.3.2 Antioxidant effects

Oxidative stress is a central component of ARMD pathophysiology. The retina is particularly vulnerable because of its high oxygen consumption, abundance of polyunsaturated fatty acids and continuous exposure to light. RPE mitochondria are important sources and targets of oxidative injury. []Although antioxidant effects have been reported for several Ayurvedic *Rasayana* drugs, there is currently insufficient evidence to state that ***Shirovirechana*** **may potentially influence neurovascular and stress-response pathways; whether such effects alter retinal antioxidant defenses requires experimental investigation.**

5.3.3 Choroidal circulation

The choroid provides oxygen and nutrients to the outer retina and RPE, and abnormalities in the RPE–Bruch's membrane–choroidal complex are important in ARMD. []However, direct evidence that *Shirovirechana* increases choroidal blood flow through modulation of nitric oxide (NO) and endothelin-1 has not been demonstrated. Therefore, NO/ET-1 modulation should be considered a **candidate mechanistic pathway for future investigation**, not an established effect.

5.4 Convergence on RPE Survival Pathways

The RPE represents a major site of pathological interaction between oxidative stress, mitochondrial dysfunction, lipid accumulation, inflammation and cellular senescence in AMD. Lipofuscin accumulation is particularly relevant because the RPE continuously phagocytoses photoreceptor outer segments. With ageing, incomplete degradation of photoreceptor-derived material contributes to lipofuscin accumulation. The bis-retinoid A2E is an important component of RPE lipofuscin and can participate in photo-oxidative injury and inflammasome activation. [3, 17]Oxidative stress and mitochondrial dysfunction may further amplify RPE injury, while damaged cellular components and drusen-associated signals can activate innate inflammatory pathways, including the NLRP3 inflammasome. [17, 18]

6. Role of *Rasayana* in Retinal Protection

Rasayana may complement the proposed role of *Shodhana* by supporting antioxidant defense, cellular resilience and healthy ageing. Evidence from human studies of selected *Rasayana* drugs supports effects on systemic oxidative-stress biomarkers. For example, a controlled study in healthy volunteers reported increased SOD and decreased MDA following administration of *Ashwagandha* and *Guduchi*. [23]

6.1 Antioxidant enhancement

The potential antioxidant action of *Rasayana* is particularly relevant to AMD because oxidative stress contributes to RPE dysfunction and photoreceptor injury. SOD, catalase, glutathione and related antioxidant systems participate in cellular ROS detoxification. [23]

6.2 Mitochondrial protection

RPE cells possess high metabolic demands and depend heavily on mitochondrial function. Mitochondrial ROS, mtDNA damage and impaired energy metabolism have been implicated in RPE ageing and AMD. [23]Therefore, antioxidant interventions may theoretically preserve mitochondrial function and cellular energy metabolism. Direct evidence demonstrating that *Rasayana* prevents mitochondrial degeneration in human ARMD, however, remains unavailable.

6.3 Anti-inflammatory activity

Inflammatory pathways including NF-κB and NLRP3 are involved in ARMD-associated retinal inflammation. [23] Selected Ayurvedic medicinal plants have demonstrated anti-inflammatory effects in experimental models. Nevertheless, the effects of a particular *Rasayana* preparation on IL-6, TNF-α or NLRP3 should only be claimed when supported by drug-specific experimental evidence.

6.4 Cellular ageing and senescence

Age-related accumulation of oxidative and mitochondrial damage can contribute to RPE cellular senescence. Consequently, modulation of antioxidant and cellular stress-response pathways may theoretically support RPE survival. This provides a rationale for investigating *Rasayana* in relation to cellular senescence, DNA damage and repair pathways, but these mechanisms require validation in retinal models.

6.5 Photoreceptor–RPE protection

Because RPE dysfunction directly compromises photoreceptor maintenance, reduction of oxidative and inflammatory injury may theoretically preserve photoreceptor–RPE interactions. This provides a

biologically plausible basis for investigating *Rasayana* as a retinal-supportive intervention, but it should not be interpreted as demonstrated clinical efficacy in ARMD.

Discussion

The available evidence provides a biologically plausible framework for investigating the relationship between Ayurvedic *Shodhana–Rasayana* interventions and mechanisms relevant to AMD. However, the evidence does not currently establish that *Virechana* or *Shirovirechana* directly modifies the molecular pathogenesis of AMD.

The strongest biomedical rationale arises from the recognized contribution of **oxidative stress, RPE dysfunction, mitochondrial injury, lipid accumulation, chronic inflammation and inflammasome activation** to ARMD. In parallel, emerging research on the gut–retina axis suggests that systemic metabolic and immune factors may influence retinal homeostasis.

Within this framework, *Virechana* may be investigated as a potential systemic metabolic intervention. Clinical evidence indicates that *Virechana* can influence lipid parameters in dyslipidemia, particularly triglycerides, but these studies were not conducted in ARMD populations. [16] Therefore, the relevance of these findings to ARMD remains indirect.

Shirovirechana presents a different mechanistic possibility because the nasal route has established anatomical and pharmacological connections with olfactory and trigeminal pathways. [17] Nevertheless, evidence is insufficient to conclude that *Shirovirechana* produces direct retinal drug delivery, increases retinal antioxidant enzymes or improves choroidal perfusion. These should be formulated as **testable hypotheses**.

Rasayana provides the most readily supportable connection with oxidative-stress biology. Human evidence involving selected *Rasayana* drugs has demonstrated changes in SOD and MDA, while experimental evidence for individual plants such as *Emblica officinalis* suggests effects on oxidative-stress and Nrf2-related pathways. [23] Nevertheless, these findings cannot be directly extrapolated to Triphala Ghrita or to clinical ARMD without retinal-specific studies.

Consequently, the proposed model is best viewed as a **translational research framework** rather than a proven therapeutic pathway. Future studies should evaluate objective biomedical outcomes including lipid profile, fasting glucose/HbA1c, hs-CRP, IL-6, TNF-α, oxidative-stress markers such as MDA, SOD and GSH, mitochondrial biomarkers, inflammatory pathways, OCT/OCTA parameters, choroidal thickness, choriocapillaris characteristics and functional visual outcomes.

Conclusion

ARMD is a complex age-associated retinal degenerative disorder in which oxidative stress,

mitochondrial dysfunction, lipid dysregulation, chronic inflammation, complement activation, RPE dysfunction and cellular senescence interact to produce progressive retinal injury. The present integrative review indicates that these mechanisms provide a scientifically relevant framework for investigating Ayurvedic *Shodhana* and *Rasayana*, but the existing evidence does not establish their efficacy in preventing or treating ARMD.

Among the proposed interventions, *Virechana* may be considered primarily from a systemic metabolic and inflammatory perspective. Existing Ayurvedic clinical studies suggest that *Virechana* can influence selected metabolic parameters, particularly lipid profiles, but these observations originate largely from non-AMD populations. Therefore, it cannot currently be concluded that such systemic effects translate into reduced drusen formation, improved Bruch's membrane function or protection of RPE cells.

Shirovirechana provides a potentially distinct nasal neurovascular pathway for investigation. Anatomical and pharmacological evidence supports communication between nasal structures and the central nervous system through olfactory and trigeminal pathways. Nevertheless, claims regarding direct delivery to the retina, improvement of choroidal circulation, modulation of ocular nitric oxide/endothelin pathways or direct retinal antioxidant effects remain hypothetical and require experimental confirmation.

Rasayana offers a comparatively stronger conceptual connection with the biology of oxidative stress and healthy ageing. Studies of selected *Rasayana* drugs have demonstrated antioxidant and anti-inflammatory effects, including changes in SOD and MDA. These findings provide a rationale for investigating their possible effects on RPE oxidative injury, mitochondrial function, inflammatory signaling and cellular senescence. However, systemic antioxidant effects cannot automatically be extrapolated to retinal protection or clinical benefit in ARMD.

Thus, the proposed *Shodhana–Rasayana* model should be regarded as a translational research hypothesis rather than an established therapeutic pathway. Its principal value at present lies in generating testable research questions linking Ayurvedic concepts with measurable biomedical outcomes. Future investigations integrating Ayurvedic clinical methodology with retinal imaging, molecular biomarkers and cellular models may determine whether these traditional interventions have genuine retinal-protective effects.

Future Research Gap

The principal research gap is the absence of a validated translational pathway connecting *Shodhana–Rasayana* interventions with retinal-specific outcomes in ARMD. Although oxidative stress, mitochondrial dysfunction, inflammation, metabolic dysregulation and cellular senescence are established components of AMD pathogenesis, evidence that *Virechana*, *Shirovirechana* or *Rasayana* directly modulate these pathways within the RPE–Bruch's membrane–choriocapillaris complex remains

insufficient. Current evidence is predominantly indirect and derived from systemic metabolic studies, experimental pharmacology or non-AMD populations. In particular, the effects of these interventions on retinal oxidative biomarkers, mitochondrial function, NLRP3/NF-κB signaling, complement activation, gut–retina interactions, choroidal perfusion and RPE/photoreceptor survival remain largely unexplored. Therefore, standardized preclinical models followed by adequately powered clinical trials incorporating molecular biomarkers, OCT/OCTA parameters and functional visual outcomes are required to determine whether the proposed *Shodhana–Rasayana* model represents a genuine retinal-protective mechanism or a biologically plausible but invalidated hypothesis.

References

1. Wong WL, Su X, Li X, Cheung CM, Klein R, Cheng CY, Wong TY. Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: a systematic review and meta-analysis. Lancet Glob Health. 2014 Feb; 2(2):e106-16. Doi: 10.1016/S2214-109X (13)70145-1. Epub 2014 Jan 3. PMID: 25104651.
2. Hamati J, Prashanthi S, Narayanan R, Sahoo N, Das AV, Rani PK, Behera UC, Khanna R, Murthy GVS. Prevalence of age-related macular degeneration and associated factors in Indian cohort in a tertiary care setting. Indian J Ophthalmol. 2023 Oct; 71(10):3361-3366. Doi: 10.4103/IJO.IJO_199_23. PMID: 37787236; PMCID: PMC10683692.
3. Mathenge W. Age-related macular degeneration. Community Eye Health. 2014; 27(87):49-50. PMID: 25918464; PMCID: PMC4322741.
4. (https://www.sciencedirect.com/science/article/pii/S0140673622026095)
5. Somasundaran S, Constable IJ, Mellough CB, Carvalho LS. Retinal pigment epithelium and age-related macular degeneration: A review of major disease mechanisms. Clin Exp Ophthalmol. 2020 Nov; 48(8):1043-1056. Doi: 10.1111/ceo.13834. Epub 2020 Aug 17. PMID: 32710488; PMCID: PMC7754492.
6. Mimura T, Noma H. Title Oxidative Stress in Age-Related Macular Degeneration: From Molecular Mechanisms to Emerging Therapeutic Targets. Antioxidants (Basel). 2025 Oct 18; 14(10):1251. Doi: 10.3390/antiox14101251. PMID: 41154560; PMCID: PMC12561695.
7. Bilbao-Malavé V, González-Zamora J, de la Puente M, Recalde S, Fernandez-Robredo P, Hernandez M, Layana AG, Saenz de Viteri M. Mitochondrial Dysfunction and Endoplasmic Reticulum Stress in Age Related Macular Degeneration, Role in Pathophysiology, and Possible New Therapeutic Strategies. Antioxidants (Basel). 2021 Jul 23; 10(8):1170. Doi: 10.3390/antiox10081170. PMID: 34439418; PMCID: PMC8388889.

8. S.N.R. Role of *Virechana* in Sharat Rutu for Prevention of Pitta Prakopa Janya Vikara. JAHM [Internet]. 2021Mar.7 [cited 2026Aug.25]; 3(2). Available from: https://www.jahm.co.in/index.php/jahm/article/view/232
9. Pt. Hari Sadasiva Sastri Paradakara, Astangahrdaya,Commentary by Arunadatta (Sarvangsundara) and Hemadri (Ayurved*rasayana*), published by Chaukhambha Sanskrit Sansthan, Varanasi,2020, Sutrasthana, Adhyay 20.
10. Taywade H, kuikarni S. Review of nasya karma and itâ€™s mode of action: Array. Ayurline [Internet]. 2017 Sep. 12 [cited 2026 Aug. 25]; 1(04). Available from: https://mail.ayurline.in/index.php/ayurline/article/view/78
11. Toma C, De Cillà S, Palumbo A, Garhwal DP, Grossini E. Oxidative and Nitrosative Stress in Age-Related Macular Degeneration: A Review of Their Role in Different Stages of Disease. Antioxidants (Basel). 2021 Apr 23; 10(5):653. Doi: 10.3390/antiox10050653. PMID: 33922463; PMCID: PMC8145578.
12. Brito M, Sorbier C, Mignet N, Boudy V, Borchard G, Vacher G. Understanding the Impact of Polyunsaturated Fatty Acids on Age-Related Macular Degeneration: A Review. Int J Mol Sci. 2024 Apr 7; 25(7):4099. Doi: 10.3390/ijms25074099. PMID: 38612907; PMCID: PMC11012607.
13. Jiang F, Ma J, Lei C, Zhang Y, and Zhang M. Age-Related Macular Degeneration: Cellular and Molecular Signaling Mechanisms. Int J Mol Sci. 2025 Jun 26; 26(13):6174. Doi: 10.3390/ijms26136174. PMID: 40649951; PMCID: PMC12249930.
14. Bilbao-Malavé V, González-Zamora J, de la Puente M, Recalde S, Fernandez-Robredo P, Hernandez M, Layana AG, Saenz de Viteri M. Mitochondrial Dysfunction and Endoplasmic Reticulum Stress in Age Related Macular Degeneration, Role in Pathophysiology, and Possible New Therapeutic Strategies. Antioxidants (Basel). 2021 Jul 23; 10(8):1170. Doi: 10.3390/antiox10081170. PMID: 34439418; PMCID: PMC8388889.
15. Zhu M, Yu W. The role of NLRP3 inflammasome in age-related macular degeneration: mechanisms and therapeutic prospects. Front Aging Neurosci. 2026 Jul 16; 18:1817987. Doi: 10.3389/fnagi.2026.1817987. PMID: 42534834; PMCID: PMC13422225.
16. Chaturvedi A, Nath G, Yadav VB, Antiwal M, Shakya N, Swathi C, Singh JP. A clinical study on *Virechana Karma* (therapeutic purgation) over the gut flora with special reference to obesity. Ayu. 2019 Jul-Sep; 40(3):179-184. Doi: 10.4103/ayu.AYU_302_19. Epub 2020 Aug 8. PMID: 33281395; PMCID: PMC7685265.
17. Sobiesk JL, Munakomi S. Anatomy, Head and Neck, Nasal Cavity. [Updated 2023 Jul 24]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2026 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK544232/?utm_source=chatgpt.com

18. Lochhead JJ, Davis TP. Perivascular and Perineural Pathways Involved in Brain Delivery and Distribution of Drugs after Intranasal Administration. Pharmaceutics. 2019 Nov 12; 11(11):598. Doi: 10.3390/pharmaceutics11110598. PMID: 31726721; PMCID: PMC6921024.
19. Bičanić I, Hladnik A, Džaja D, Petanjek Z. THE ANATOMY OF OROFACIAL INNERVATION. Acta Clin Croat. 2019 Jun; 58(Suppl 1):35-42. Doi: 10.20471/acc.2019.58.s1.05. PMID: 31741557; PMCID: PMC6813484.
20. Ochoa Hernández ME, Lewis-Luján LM, Burboa Zazueta MG, Del Castillo Castro T, De La Re Vega E, Gálvez-Ruiz JC, Trujillo-López S, López Torres MA, Iloki-Assanga SB. Role of Oxidative Stress and Inflammation in Age Related Macular Degeneration: Insights into the Retinal Pigment Epithelium (RPE). Int J Mol Sci. 2025 Apr 8; 26(8):3463. Doi: 10.3390/ijms26083463. PMID: 40331961; PMCID: PMC12026614.
21. Kauppinen A, Paterno JJ, Blasiak J, Salminen A, Kaarniranta K. Inflammation and its role in age-related macular degeneration. Cell Mol Life Sci. 2016 May; 73(9):1765-86. Doi: 10.1007/s00018-016-2147-8. Epub 2016 Feb 6. PMID: 26852158; PMCID: PMC4819943.
22. Shukla SD, Bhavnagar M, Khurana S. Critical evaluation of ayurvedic plants for stimulating intrinsic antioxidant response. Front Neurosci. 2012 Jul 26; 6:112. Doi: 10.3389/fnins.2012.00112. PMID: 22855669; PMCID: PMC3405414.
23. Kuchewar VV, Borkar MA, Nisargandha MA. Evaluation of antioxidant potential of *Rasayana* drugs in healthy human volunteers. Ayu. 2014 Jan; 35(1):46-9. Doi: 10.4103/0974-8520.141919. PMID: 25364199; PMCID: PMC4213967.
24. Kaarniranta K, Uusitalo H, Blasiak J, Felszeghy S, Kannan R, Kauppinen A, Salminen A, Sinha D, Ferrington D. Mechanisms of mitochondrial dysfunction and their impact on age-related macular degeneration. Prog Retin Eye Res. 2020 Nov; 79:100858. Doi: 10.1016/j.preteyeres.2020.100858. Epub 2020 Apr 13. PMID: 32298788; PMCID: PMC7650008.
25. Ruan Y, Jiang S, Gericke A. Age-Related Macular Degeneration: Role of Oxidative Stress and Blood Vessels. Int J Mol Sci. 2021 Jan 28; 22(3):1296. Doi: 10.3390/ijms22031296. PMID: 33525498; PMCID: PMC7866075.