



## Of Vanishing Retinal Drusen and Oxysterols

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All authors contributed equally in the creation and revision of this mini-review. All authors read and approved the final manuscript.

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### ABSTRACT

**Aim:** Spontaneous resolution of retinal drusen is a common occurrence in ophthalmology, but little is understood about the mechanistic pathophysiology of this phenomenon. Small molecules, taken orally, such as resveratrol (RV) and zeaxanthin (Z), resolve retinal drusen and amyloid protein, yet few clinicians are aware of this molecular, biochemical progress against the major degenerative disease(s) of ageing.

**Published Data:** We highlight the mechanistic role of resveratrol (RV) in the cytochrome P450 enzymatic pathways of liver detoxification, as well as dosing considerations. RV has demonstrated utility in age-related macular degeneration (AMD) and has application in disorders of cognition (Alzheimer's Disease) and age-related hearing loss. We highlight the clinical evidence for the use of an epigenetic RV nutraceutical matrix called Longevinex®, and the xanthophyll carotenoid zeaxanthin. Longevinex® has been employed against retinal drusen, with resulting normalisation of retinal anatomy, Amsler Grid field loss (scotomas) and distortions of the central visual field (metamorphopsia).

**Implications:** The published evidence for RV and Z resolving structural and functional deficits in

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AMD is presented. The xanthophyll carotenoid zeaxanthin has now been demonstrated, in a larger population clinical trial, to resolve drusen beyond normal expectation. Both RV and Z have also both shown to induce denser macular pigment, and such small molecules likely play a role in multisensory degeneration(s) of ageing.

**Conclusion:** Previously described "spontaneous resolution" of drusen may have an unappreciated biological mechanism(s). The adjunct and complimentary wound healing benefits of RV and Z remain clinically underutilised in age-related retinal and neuro-degeneration associated diseases of ageing, while the complications of chronic ophthalmologic anti-vascular endothelial growth factor intravitreal injections emerge as problematic.

**Keywords:** Ageing; age-related macular degeneration (AMD); drusen; epigenetics; Longevinex®; oxysterols; resveratrol; statins and zeaxanthin.

## 1. INTRODUCTION

Case reports and open case studies in modern medicine are of value for a number of reasons: [1] they can point towards a new direction in therapeutic or preventive medicine; [2] they can reveal underlying biological mechanisms that require further exploration; [3] they may provoke pilot studies and go on to initiate controlled human studies; [4] they may be of value in aiding clinicians who deal with patients having rare diseases and disorders for which no controlled studies are possible; [5] they involve individual subjects in the real clinical world who take combinations of medications and other therapies not factored in controlled studies.

As background information, drusen, derived from the German word for *geode*, are tiny yellow or white inflammatory waste deposits that build up in Bruch's membrane and the retinal pigment epithelium layers of the retina. These deposits are visualised by eye doctors during the ophthalmoscopic examination. The presence of larger and more numerous drusen in the macula is a sentinel sign of age-related macular degeneration (AMD), the leading cause of blindness in ageing western societies. Even lesser degrees of AMD make it difficult to read, drive and recognise faces - all activities of daily life.

Drusen are comprised of lipid, protein, and inflammatory mediators, as well as oxysterols. The latter is a derivative of cholesterol, which comprise 40% of drusen content [1]. Several studies have shown that oxysterols, which accumulate with the ageing of oxidised lipoproteins, have cytotoxic and pro-inflammatory characteristics eventually resulting in apoptosis of retinal pigment epithelial (RPE) cells [2]. Amyloid beta, which builds up in Alzheimer's brains, is a notable protein that accumulates in

drusen, and cerebral tissue. Therefore, AMD is sometimes called "Alzheimer's of the eye" or "Alzheimer's of the retina" [3].

The liver plays an outsize role in the detoxification through two phases of metabolism, Phase 1 and Phase 2 detoxification.

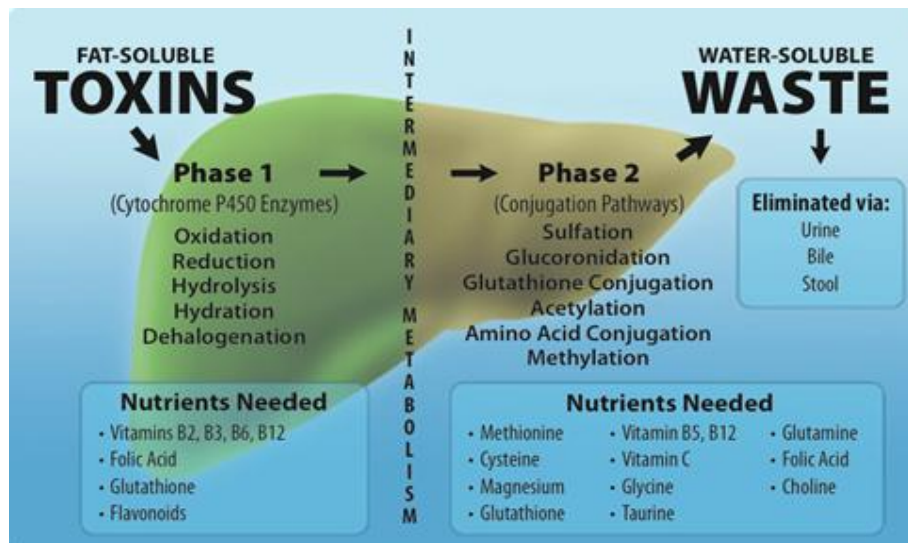
The variability of human CYP450 enzymes provides a wide array of response to xenobiotic(s) depending upon the genetic expression of the specific CYP450 enzyme(s). Knowledge of an individual's CYP450 variants, as well as the interactions of different nutrients upon the CPY450 variant(s), is one basis for personalised medicine [5]. Only 6 of the 50+ known cytochrome P450 enzymes account for more than 90 percent of all drug metabolism [6]. Resveratrol (RV) has been implicated in the functionality of four of these major enzymes (CYP1A, CYP2C9, CYP2D6 and CYP3A) along with another key enzyme in cholesterol metabolism (CYP27A1). This is the main reason why RV is widely known to modulate the effects of drugs. Table 1 summarises the functions of these liver enzymes and their interactions with RV [7].

During *phase II metabolism*, the now transformed xenobiotic becomes conjugated with hydrophilic compounds, such as glucuronic acid, sulfate, glutathione, amino acids, acetyl groups, and methyl groups through transferases. The purpose of the transferases is to make the xenobiotic more hydrophilic for disposal (of the transformed xenobiotic) through bile or urine. Genetic transferase variations also lead to variability in the efficacy of these transferases [5].

RV has been demonstrated to play a key role in the modulation of important phase 1 and 2 liver detoxification and metabolism reactions. Specific phase I biotransformation enzymes from

cytochrome P450 and its isoforms can convert otherwise innocuous, non-cancerous molecules into carcinogens [5]. RV can alter the activity of

these phase 1 enzymes by limiting the activation of procarcinogens, potentially establishing itself as an anti-cancer agent in the process [8].



**Fig. 1. Phase 1 and Phase 2 liver metabolism. The first phase involves cytochrome P450 (CYP450) enzymes, while the second phase of metabolism involves conjugation enzymes [4]. Phase 1 metabolism commonly acts as the first line of defence towards metabolizing xenobiotics and uses the heme group of the cytochrome P450 family to perform a series of reactions aimed at making the compound more hydrophilic through the addition of a reactive group [5,4] Notably, the reaction with CYP450 enzymes involves oxidation, reduction, and hydrolysis [5] Summary Figure Source Attribution: Nate Freeman, ©Ortho Molecular Products. <https://www.orthomolecularproducts.com/>**

**Table 1. Cytochrome P450 enzyme - RV Interaction: [5,7] The most important mechanisms for this discussion are highlighted in 'red'**

Cytochrome P450 Enzyme	Mechanism / Significance	Resveratrol Interaction
<b>CYP1A</b>	Metabolism of procarcinogens, hormones, xenobiotics	Resveratrol weakly induces expression, thereby increasing clearance of certain medications below therapeutic threshold
<b>CYP2A</b>	Metabolism of xenobiotics, hormones, and endogenous compounds such as fatty acids and glycerol	Resveratrol lowers its activity, leading to a reduction in the incidence of testicular cancer
<b>CYP2C, CYP2D</b>	Metabolism of xenobiotics such as warfarin and metoprolol	Resveratrol decreases enzymatic activity, potentially lowering the therapeutic effect of stated drugs
<b>CYP3A</b>	The main cytochrome enzyme responsible for the metabolism of more than 50% of all xenobiotics	Resveratrol decreases enzymatic activity, potentially lowering the therapeutic effect of stated drugs
<b>CYP27A1</b>	Facilitates disposal or efflux of cholesterol byproducts (oxysterols) via release from macrophages and excretion via bile flow	Resveratrol activates CYP27A1 and may be implicated in the resolution of oxysterol deposits such as drusen

Statins inhibit production of cholesterol via inhibition of the HMG-CoA reductase enzyme in the liver. Its mechanism of action has been used to treat AMD incidence and progression. In a recent 12-month study, 10 out of 23 patients who took atorvastatin had a decrease in drusen deposits associated with vision gain [9]. In contradistinction, RV (and the polyphenolic-based (red wine solids) nutraceutical matrix Longevinex®) activates the cytochrome p450 sterol 27-hydroxylase (CYP27A1) enzyme to facilitate the disposal or efflux of cholesterol byproducts (oxysterols) (Fig. 2 and Table 1) [10].

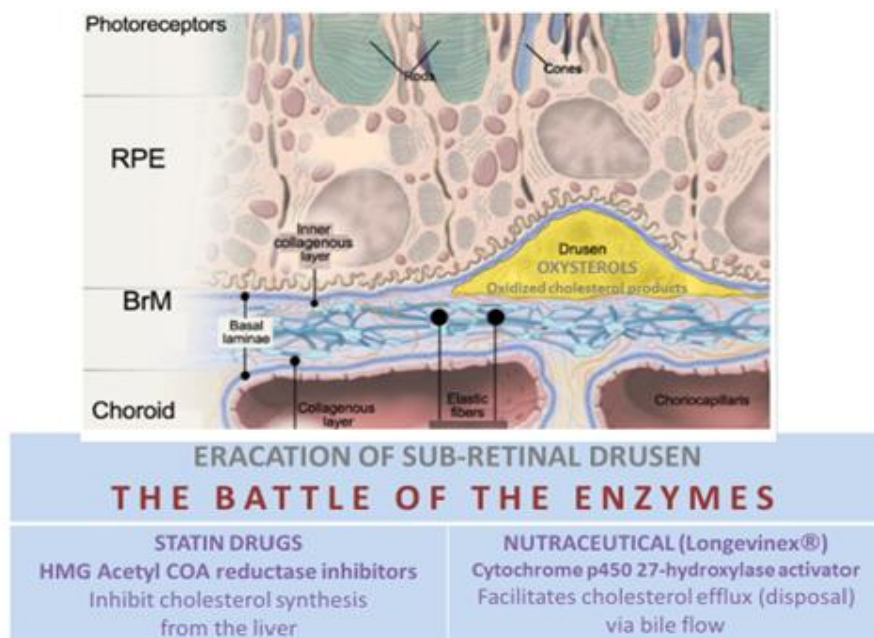
prudent to establish a safe clinical dosing. RV is not considered toxic in humans at therapeutic levels below 1000 mg per day [13,14]. Although RV dosing at 1000 mg per day is reportedly well tolerated in healthy individuals, mega dose RV inhibits sulfotransferase enzymes that attenuate adrenal stress hormones [15,16]. Overdosing can result in a racing heart, anxiety reactions, skin rash, and flu-like symptoms akin to those experienced with TNF-inhibiting drugs, RV being a natural TNF inhibitor [17, 18]. There are also reported cases of Achilles heel tendonitis with mega-dose RV [17].

Also, RV modulates many of the important phase II detoxification enzymes generally leading to detoxification of active carcinogens [7,12]. RV accomplishes this through the activation of UDP glucuronosyltransferase (UGT), glutathione S-transferase (GST), and quinone reductase (QR) activity via mitogen-activated protein kinase pathways. These effects are magnified in patients with endogenous low baseline enzymes [7].

Recent research indicates as little as 10 to 25 mg provides cardioprotective benefit following myocardial infarction and reduces cancer progression without inducing negative effects that may result when dosing becomes too high (5000 mg per kg of body weight daily results in nephrotoxicity when evaluated by Glaxo SmithKline / Sirtris Pharmaceuticals) [19,20]. Future research should consider optimal dosing, especially in patients taking drugs metabolised by enzymes that interact with RV. This will maximise the positive effects while allowing for proper metabolism of clinical medications [7].

## 2. RV DOSING CONSIDERATIONS

RV is increasingly utilised in cancer, cardiology, neuroscience, and ophthalmology research. It is



**Fig. 2. Drusen / Oxysterol Clearing: A comparison between statin drugs and nutraceuticals (i.e., Longevinex®) by mechanism [11]. Statin pharmaceuticals inhibit the synthesis and influx of cholesterol, while RV facilitates its efflux via bile flow.**

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### **3. AMYLOID REDUCTION AND MODULATION IN ALZHEIMER'S DISEASE (AD)**

Heavy redox reactive metals such as free and unbound redox reactive labile  $\text{Cu}^{2+}$  and  $\text{Fe}^{2+}$  have a high affinity for amyloid- $\beta$  peptides ( $\text{A}\beta$ ), causing accumulation of this toxin in the brain.  $\text{Cu}^{2+}$  and  $\text{Fe}^{2+}$  also promote retinal drusen, by damaging cholesterol cellular efflux. Retinal drusen that contain  $\text{A}\beta$  likely have significance in the development of other diseases [21].

RV may assist patients suffering from early cognitive decline and the more advanced stages of AD. Analogous to retinal drusen, aggregation of neurotoxic  $\text{A}\beta$  in the brain is believed to be an intermediate and long-term marker. Caloric restriction benefits longevity by slowing ageing. Research in small organisms shows that RV extends lifespan by delaying certain age-related phenotypes such as defective glucose metabolism. Indeed, patients with diabetes are at increased risk of AD (Diabetes Type III). Due to caloric restriction mimicry, RV may benefit mild cognitive impairment and early AD by directly impacting the rate of cognitive deterioration by modulating glucose metabolism [22].

RV is available in very low mg concentrations among foods such as red wine and within the skins of red grapes and peanuts. However, this is not sufficient to reach the minimum threshold needed to activate RV's neurological health benefits. Currently, the mechanism of RV's direct action in the brain is unknown, however, it does involve metabolic proteins, such as AMP-activated kinase (AMPK), sirtuin 1 (SIRT1), and peroxisome proliferator-activated receptor  $\gamma$  coactivator-1 $\alpha$  (PGC-1 $\alpha$ ). SIRT1 is notably necessary for RV's actions on metabolic function. AMPK and PGC-1 $\alpha$  are further involved in that metabolic network [22].

RV aids in the clearance of  $\text{A}\beta$  peptides in vitro [23].  $\text{A}\beta$  peptides are formed by the actions of two enzymes,  $\beta$ -secretase and  $\gamma$ -secretase. However, when the amyloid precursor protein (APP) is cleaved by  $\alpha$ -secretase specifically at the  $\text{A}\beta$  sequence,  $\text{A}\beta$  peptide production is halted. Studies have shown that caloric restriction decreases production of  $\text{A}\beta$  peptides by promoting the  $\alpha$ -secretase pathway, preventing APP from being processed by  $\beta$ -secretase and  $\gamma$ -secretase [22,23] Similar studies show SIRT1 expression is increased during caloric restriction, in turn leading to reduced

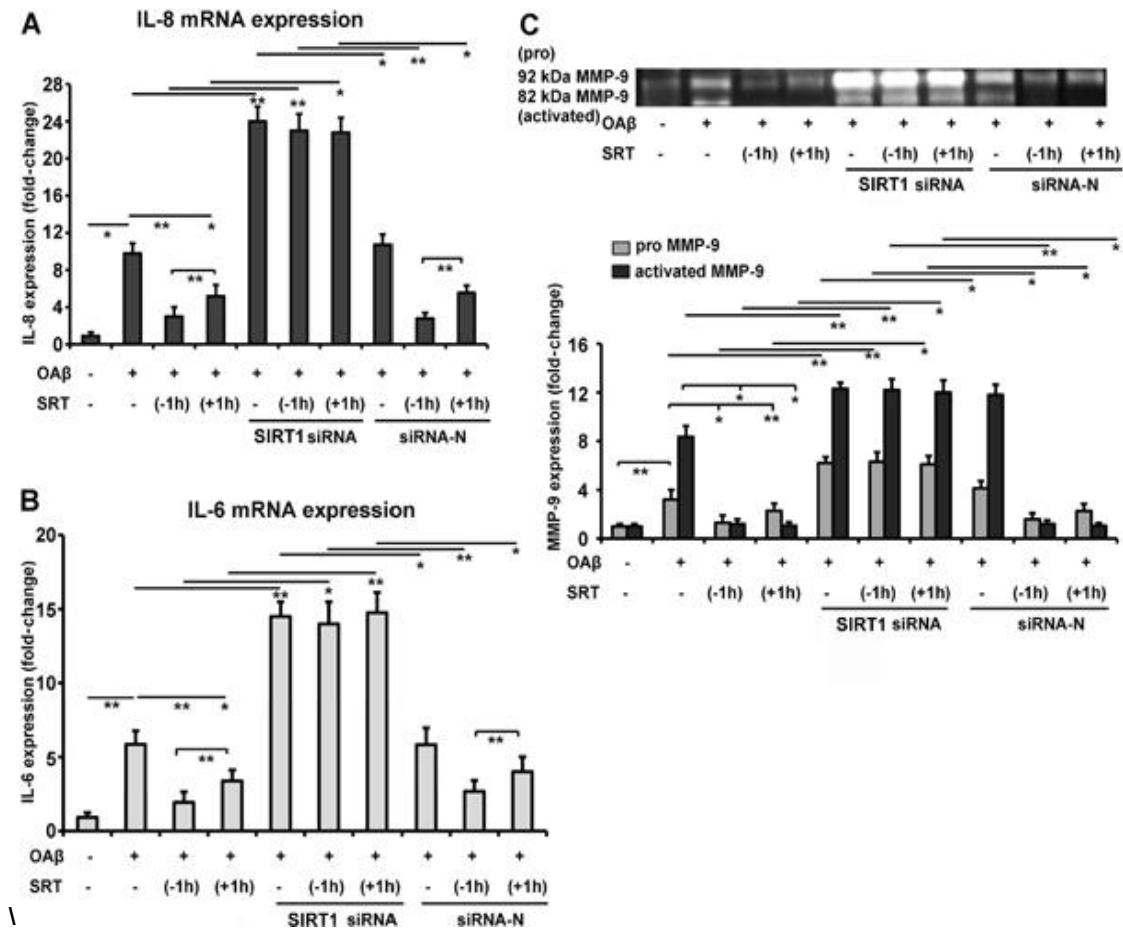
production of  $\text{A}\beta$  peptides by increasing  $\alpha$ -secretase pathway activity [23,24] Qin et al. found that SIRT1 expression and NAD<sup>+</sup> levels are increased in Tg2576 transgenic mice by enabling  $\alpha$ -secretase, resulting in reduced  $\text{A}\beta$  peptide production. The team's study in squirrel monkeys confirmed this finding when they established that calorie restriction reduces  $\text{A}\beta$  peptide production, an increased localised brain SIRT1 concentration [25].

In summary, RV-associated basic science, along with our limited clinical experience, suggests a safe method to both prevent  $\text{A}\beta$  peptide production and its sequential deposition in the brain while enhancing retinal structure and function and possibly other senses that decline with age [22].

### **4. AMYLOID IN AMD AND THE RV MODULATED SIRT-1 SURVIVAL GENE**

In addition to being a hallmark of AD,  $\text{A}\beta$  is also a component in retinal drusen that is thought to influence the development of AMD. The pathogenesis of AMD involves chronic inflammation of the retina associated with the accumulation of cytokines such as matrix metalloproteinase-9 (MMP-9), interleukin-6 (IL-6), and interleukin-8 (IL-8). Studies show that the upregulation of  $\text{A}\beta$  peptide production stimulated IL-8 gene expression. IL-8 is a significant chemokine mediator in inflammation that recruits neutrophils and promotes their degranulation, thus linking  $\text{A}\beta$  to AMD through common proinflammatory pathways that, if regulated, can reduce deterioration of the retina in patients with AMD [26].

One of the regulators of the inflammatory response involves the acetylation of nuclear factor-kappa B (NF- $\kappa$ B). SIRT1 functions as a deacetylating agent that halts the inflammatory cascade by inhibiting NF- $\kappa$ B. As discussed previously, SIRT1 has an important role in reducing the production of  $\text{A}\beta$  peptides. This furthers our insight into SIRT1's effect on the reduction of  $\text{A}\beta$  peptides and subsequent inflammation of the retina in patients suffering from AMD. In a study by Cao et al., human RPE cells were harvested from donors, and SIRT1 gene expression was silenced by RNA interference. When treated with  $\text{A}\beta$ , the RPE cells began to produce IL-8, IL-6, and MMP-9. In RPE cells with the SIRT1 knockout,  $\text{A}\beta$  induces even more cytokines to be released. SRT1720, a SIRT1 agonist, is used to explore SIRT1's effect



**Fig. 3a, b, c.** The effects of A $\beta$ , SIRT1, and SRT1720 on the expression of multiple proinflammatory mediators in human RPE cells. Repressing SIRT1 gene expression by RNA interference via SIRT1 siRNA shows a significant increase in proinflammatory IL-8, IL-6, and MMP-9 activity after exposure to A $\beta$ . RPE cells were also exposed to SRT1720. However, SRT1720 reduces the production of inflammatory cytokines, only in the presence of an active SIRT1 gene [26]. *Note*, 1-hour pre-treatment with SRT1720 decreases cytokine expression better than 1-hour post- SRT1720 treatment. Attribution

<http://www.scielo.br/img/revistas/bjmr/v46n8/1414-431X-bjmr-46-8-659-gf003.jpg>

on the RPE cells. When SRT1720 was used on cells without the silenced SIRT1 gene, A $\beta$  induced expression of IL-8, IL-6, and MMP-9 is significantly reduced. This phenomenon was replicated in cells with the SIRT1 knockout, giving the same result. Protein extraction and western blotting revealed that SIRT1 gene activation was necessary to protect the RPE from A $\beta$  induced expression of IL-8, IL-6, and MMP-9 (See Fig. 3a, b and c) [26].

Due to the polyphenol's ability to mimic calorie restriction, RV has been previously shown to indirectly increase SIRT1 expression, thereby reducing A $\beta$  production [22]. This highlights the

connection between AMD and AD and how future research can further facilitate RV's potential as an effective nootropic nutraceutical.

### 5. EYE AND BRAIN CLINICAL RV DATA

We have published previous case reports that involve resolution of retinal drusen and improvement in multiple aspects of visual function, such as enhanced visual acuity, contrast sensitivity, glare recovery and denser macular pigment [21,27]. Subsequently, the SD-OCT (spectral-domain ocular coherence tomography images), as well as an image

showing stem cell RPE regeneration were published in two medical textbooks [21,28].

Emerging human clinical studies now support the notion of RV aiding in the reduction of AD. In a 52-week study, 119 subjects were given either 500mg – 1000 mg of RV or a placebo. While amyloid  $\beta$  proteins progressively decline in patients with dementia, subjects taking the RV treatment showed less decline of A $\beta$ 40 in cerebrospinal fluid and plasma than patients in the placebo group. The CSF matrix metalloproteinase 9 (MMP9), hypothesized to influence the blood-brain barrier permeability, was also decreased in patients taking RV. Other significant findings from the study show RV's effect of increasing chemokine, interleukin-4, and fibroblast growth factor-2 [29]. The increase in these markers support RV's induction of an adaptive immune response, aided Alzheimer's patients, by regulating further amyloid deposition [30].

The role of RV is also implicated in presbycusis, or age-related high-frequency hearing loss [31]. The molecular and biochemical mechanisms of this condition are not fully understood, and there are only minimal biochemical treatments under evaluation [31]. One theory on age-related hearing loss states that it coincides with oxidative dysfunction within mitochondria, resulting in the accumulation of reactive oxidative species that accumulate to cause cochlear cell apoptosis [32]. RV again shows promise as a treatment for the progression of age-related hearing loss via its role as a sirtuin gene activator [32,33] Research demonstrates that RV-mediated activation of SIRT1 decreases p53 acetylation and apoptosis within the cochlea, strengthening the case for its role as a potential therapeutic agent in age-related hearing loss [33].

## 6. ZEAXANTHIN AND RETINAL DRUSEN RESOLUTION

This phenomenon of unexplained spontaneous resolution of retinal drusen, the sentinel sign of AMD is not unique to Longevinex® [34]. There are other classes of nutrients such as dietary carotenoids (i.e., lutein and zeaxanthin.) playing a role in promoting CYP27A1 activity, and consequently in the elimination of the cholesterol deposits of which drusen are comprised. For example, in clinical practice, Herman et al. reported that 193 out of 196 patients who

displayed hard drusen and 115 out of 119 who displayed soft drusen on SD-OCT, showed either improvement or 'clinical stability' after a 24-month period of dietary carotenoid supplementation that included lutein and zeaxanthin [35].

This large case study (n=515 patients) highlighted the importance of the carotenoid zeaxanthin and its role in the improvement of macular pigment optical density (MPOD). Low MPOD increases the risk of AMD, while increased dietary carotenoid intake prevents AMD [36]. Zeaxanthin and lutein are the 2 dietary carotenoids found in the eye and are required for central and paracentral visual function. Subjects orally ingesting 8 mg Zeaxanthin and 4 mg lutein for 24 months showed average increases of 82.6% in MPOD with 88.3% of subjects showing at least a 30% MPOD increase. Patients also improved visual acuity, on average, from 20/30-2 to 20/25+2 and improved their Amsler Grid visual metamorphopsia improved over baseline [35].

Previous research shows zeaxanthin to function as an antioxidant in protecting cellular membrane-embedded lipids and proteins from oxidation by free radicals. This pathway is thought to involve the molecules nrf2 / keap1 in conjunction with phase II heme oxygenase enzymes. Intracellularly, zeaxanthin activates the p-Akt1 protein, which promoted the dissociation of nrf2 from keap1, allowing for nrf2 to enter the nucleus and promote the transcription of anti-apoptotic factor glutathione (GSH). The significance of this suggests zeaxanthin can prevent harmful effects of oxidative stress by lowering mitochondrial dysfunction and reducing subsequent apoptosis. This will spare the macular pigment cells, which normally decrease with age as a result of the continued oxidative stress exposure, leading to free-radical-induced apoptotic activity. Since higher amounts of macular pigment correspond with lower incidences of AMD, zeaxanthin could very well play a preventive role in AMD prevention. Zeaxanthin as well increases glutathione levels in the heart and liver. Since reduced glutathione levels have been linked to multiple diseases, including cancer, diabetes, and neurodegenerative diseases, the ability of zeaxanthin to increase cellular glutathione provides numerous benefits apart from preventing AMD [37].



**Table 2. Changes in drusen with lutein/zeaxanthin supplementation as a function of the degree of MPOD change n = 119. After Herman et al. [35]**

Soft Drusen Change ++	MPOD Change Categories			
	<= 15% n (%)	>15% to 30% n (%)	>30% n (%)	Total n (%)
Improved	1 (14.3%)	1 (9.1%)	14 (14.4%)	16 (13.9%)
Stable	6 (85.7%)	10 (90.9%)	82 (84.5%)	99 (85.2%)
Advancement	2 (<2%)	1 (<1%)	1 (<1%)	4 (3.4%)
Total Stable or Improved	7 (5.9%)	11 (9.2%)	96 (80.7%)	115 (96.6%)

<https://medcraveonline.com/AOVS/AOVS-06-00166.pdf>

**Table 3. Salutary Amsler Grid baseline metamorphopsia improvement [35]**

Baseline Finding	n=	12m Change++	24m Change++
Hard Macular Drusen with Amsler Grid Distortion	27 (5.2%)	Improved 2 (7.4%) Stable 24 (88.8%) Advanced 1 (4.0%)	Improved 16 (59.3%) Stable 11 (40.7%) Advanced 0 (0%)
Hard Paramacular Drusen with Amsler Grid Distortion	43 (8.3%)	Improved 11 (25.6%) Stable 31 (72.1%) Advanced 1 (2.3%)	Improved 17 (39.5%) Stable 26 (60.5%) Advanced 0 (0%)
Soft Drusen with RPE Changes and Amsler Grid Distortion	98 (18.8%)	Improved 21 (21.4%) Stable 74 (75.5%) Advanced 3 (3.1%)	Improved 39 (39.8%) Stable 52 (53.1%) Advanced 7 (7.1%)

<https://medcraveonline.com/AOVS/AOVS-06-00166.pdf>

## 7. IMPLICATIONS

The correlation between beta-amyloid deposition in the brain and the accumulation of drusen deposits in the human retina is significant, as is the close connection between all multisensory chronic diseases of ageing as shown in the Fig. 4.

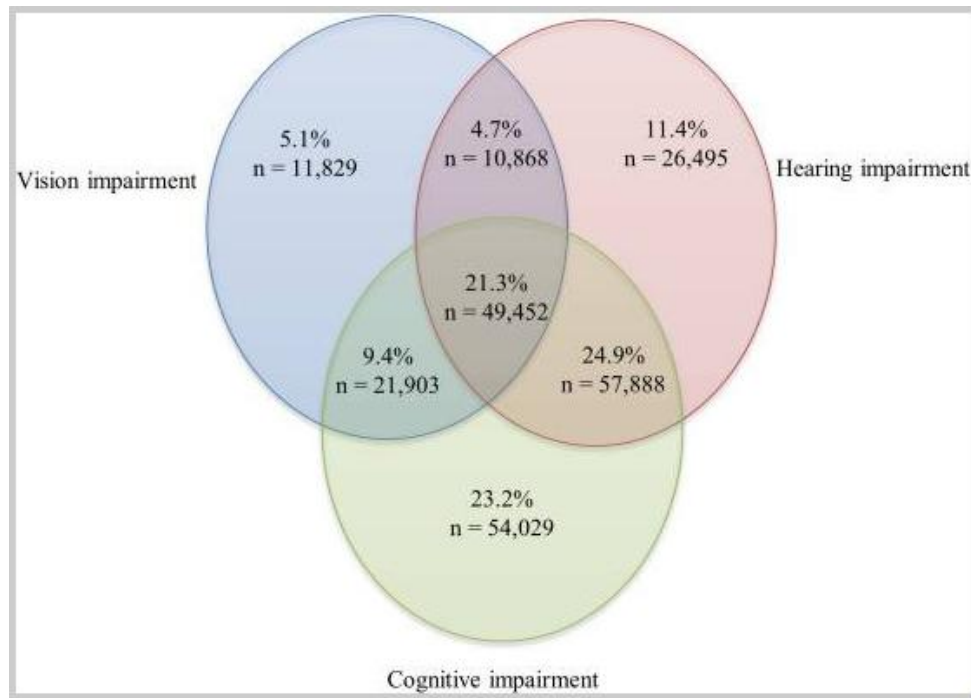
We bring to the attention of the larger medical and research community our continuing efforts to report a unique, dramatic and instructive case of reversal of retinal drusen and disease over a long-term 16-year period that encompassed various efforts of self-rescue by a one-eyed patient to avert his progressive functional blindness [21].

The patient, initially a 28-year old male with "Dominant Drusen" whose vocation required functional vision, had eventually exhausted all options by the time he began to lose vision in the prime of his life. He exhibited massive central retinal drusen, analogous to that found in AMD, and after personal investigation, the patient initiated his own choice of therapy beyond the AREDS II NEI vitamins for AMD.

As clinicians, we recognise retinal drusen wax and wane, but the long-term progression of this 'pre-disease state' did not reveal that. Instead, various dietary (weight loss regimen), medical (two different types of cholesterol-lowering drugs (statins), antioxidant (dietary supplement formulated by the US National Eye Institute), and small epigenetic nutraceutical molecules (resveratrol, quercetin, phytate + vitamin D3 + nucleotides) were utilised that provide unique insight into comparative therapies over time. While the area of the drusen-free retina as measured in pixels improved with weight control, antioxidant and statin cholesterol-lowering drug therapy, Longevinex® notably and unexpectedly accelerated further drusen dissolution and produced the only meaningful improvement in functional vision. The afflicted patient contacted our research group, as he felt such information deserved a wider audience [21].

Visual evaluation of the central retina before the use of the RV-based nutraceutical presented obvious multiple drusen deposits pock-marked throughout the central retina whereas, after use of the nutraceutical, abolishment of central retinal drusen is clearly obvious to the naked eye





**Fig. 4. Multi - sensory impairment in ageing. Combined impairments in vision, hearing, and cognition are associated with greater levels of functional and communication difficulties than cognitive impairment alone. Attribution <https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0192971>**

evaluation by SD-OCT scan [21]. That the resveratrol-based nutraceutical produced such a demonstrable improvement in functional vision and eradication of drusen from the central retina after the modest dissolution of drusen via dietary, antioxidant and statin drug intervention is of acute research and clinical interest.

Indeed, this case had provided a unique opportunity to compare these therapies, showing the patient's visual distortions only resolved when the polyphenol-based pill was employed and did so rapidly and unexpectedly. There are implications here concerning the comparative use of statins vs. nutrients in the removal of atherosclerotic plaque from blood vessels, well known to the British Journal of Medicine [38,39]. The authors have spent nearly 2 years facing a persistent and pervasive bias to bring to light such triumphs to a larger scientific audience.

## 8. CONCLUSION

Spontaneous drusen and amyloid resolution merit consideration, as there are few proven therapies for the insidious and prevalent ageing of the retina, brain and even cochlear. This mini-

review has described the potential for small nutrient molecules to simultaneously impact multisensory degenerations of ageing (vision, cognition and hearing), if we have the fortitude to address all chronic diseases of ageing disease from a common molecular medicine perspective.

The polyphenolic nutraceutical (Longevinex®) and high dose zeaxanthin resolve drusen and have elicited no reported safety concerns in over a dozen years of human use. In contradistinction, current pharmaceutical invasive intravitreal anti-VEGF AMD treatments induce a 500% increase in the destruction of the photoreceptor – RPE complex, resulting in eventual loss of vision [40].

It is estimated 15% of AMD cases fail anti-VEGF treatment. That is hundreds of thousands of patients. There is also a worrisome *increase in mortality post-treatment* [41]. Thus there is an urgent imperative to explore complementary adjunctive therapies in hopes of rescuing more patients from permanent blindness and the undesirable sequelae of traditional treatment. Increased mortality (6-fold) following anti-VEGF treatment, after a myocardial infarction, is particularly troubling and suggests anti-VEGF

treatment has systemic effects that *impair* normal wound healing [41,42]. The molecules described in this mini-review *promote* wound healing and thus should be evaluated alongside traditional therapeutic approaches.

## CONSENT

It is not applicable.

## ETHICAL APPROVAL

It is not applicable.

## ACKNOWLEDGEMENTS

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## COMPETING INTERESTS

Authors have declared that no competing interests exist. The company names used for this research are commonly and predominantly selected in our area of research and country. There is absolutely no conflict of interest between the authors and the company because we do not intend to use these companies as an avenue for any litigation but the advancement of knowledge. Also, the research was not funded by the company rather it was funded by the personal efforts of the authors. Dr Richer is global scientific director of the Zeaxanthin Trade Association.

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