ARTYKUŁ PRZEGLĄDOWY REVIEW ARTICLE
DOI: 10.24292/01.OT.300324.2

The role of resveratrol in inhibiting the development and progression of oxidative stress-induced retinal diseases

Małgorzata Figurska
Department of Ophthalmology, Military Institute of Medicine – National Research Institute in Warsaw
Head: Prof. Marek Rękas, MD, PhD

HIGHLIGHTS

A review of the current literature confirms the important beneficial role of resveratrol and dietary supplements containing resveratrol in limiting the development and progression of oxidative stress-related diseases.

ABSTRACT

In recent years, the importance of resveratrol as a biologically active natural nutrient with potential to prevent the development and progression of age-related degenerative diseases has been analyzed. The aim of the study is to review the current literature from the last 10 years or so, dealing with the subject of resveratrol properties, its impact on systemic condition and retinal diseases. This review confirms the important beneficial role of resveratrol and dietary supplements containing resveratrol in limiting the development and progression of diseases related to oxidative stress. The range of action of resveratrol is systemic, as evidenced by research. In ophthalmology, resveratrol is used primarily in degenerative retinal diseases and complications of metabolic diseases in which oxidative stress plays a key role. The data from the conducted studies provide the basis for the assumption that thanks to compounds such as resveratrol, we may gain a real impact on the occurrence of e.g. age-related macular degeneration and its course.

Key words: resveratrol, age-related macular degeneration, diabetic macular edema, oxidative stress

INTRODUCTION

Polyphenols are bioactive compounds found in plant foods. They have health-promoting properties due to their antioxidant, anti-inflammatory, immune-modulating, and gut microbiome-regulating properties. Resveratrol is a natural polyphenolic compound, a polyphenolic phytoalexin, belonging to stilbene family [1, 2]. It is found in many foods, such as grapes, peanuts, berries, seeds and red wine. Resveratrol acts by activating sirtuin 1 (SRT1) [3]. It has been found to exhibit several biological activities, including the ability to lower blood pressure, regulate lipid levels, and provide cardioprotection. Additionally, it has been shown to be effective in preventing and treating cancer, cardiovascular disease, and obesity. Additionally, resveratrol may slow down the aging process in the human body by suppressing oxidative stress, improving mitochondrial function, and modulating apoptosis. Resveratrol is generally considered a compound with positive effects on age-related diseases, including cancer, and life expectancy [4]. In recent years, researchers have studied the potential of resveratrol as a biologically active natural nutrient to prevent age-related degenerative diseases and aging processes. This article reviews the current literature from the last decade on the properties of resveratrol and its effects on systemic conditions and retinal diseases.

RESVERATROL AND ITS ROLE IN NEUROLOGICAL AND CARDIOVASCULAR DISEASES

Aging is a major risk factor for neurodegenerative diseases. It is accompanied by inflammation, dysregulated autophagy, neuronal apoptosis, and increased oxidative stress. These factors lead to progressive memory loss and motor impairment. Neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, and dementia, develop with age [5]. Studies indicate that resveratrol may offer protection against neurodegenerative diseases. Experimental studies have shown positive effects of resveratrol on hippocampal plasticity and memory function in female mice. Resveratrol promotes neurogenesis and neuronal differentiation, leading to improved behavioral performance in vivo. Mice that were treated with resveratrol exhibited an increase in phosphoprotein kinase B and phosphoprotein kinase C. Additionally, intracerebroventricular administration of resveratrol to mice for 7 days led to their long-term memory improvement and a long-term induction of hippocampal function. This effect was blocked in mice with SRT1 mutations [6]. The rising incidence of cardiovascular disease (including hypertension and vascular atherosclerosis) in developed countries has prompted research into substances that can enhance cardiovascular health. Resveratrol is believed to be a contributing factor to the "French Paradox", i.e., a phenomenon describing why cardiovascular disease is less common in people who drink more wine and follow the Mediterranean diet (fish, seafood, vegetables, fruits, oil), consume more saturated fats, and smoke. In addition to its antioxidant and anti-inflammatory properties, resveratrol has been shown to increase endothelial nitric oxide synthase (eNOS). Resveratrol has also been demonstrated to scavenge superoxide radicals, which can reduce lipid peroxidation processes. Moreover, in bovine aortic endothelial cells under glucose-induced oxidative stress, resveratrol restored the activity of dimethylarginine dimethylaminohydrolase (DDAH), an enzyme that degrades an endogenous eNOS inhibitor called asymmetric dimethylarginine (ADMA). Thus, resveratrol may improve nitric oxide availability and reduce the vascular endothelial dysfunction observed in diabetes. Human studies on resveratrol are still limited. In addition, there are difficulties in interpreting the results due to the fact that research studies use high doses of resveratrol, whereas its low concentrations are found in red wine [7–9].

RESVERATROL IN RETINAL DISEASES

Aging process is also associated with degenerative diseases of the eye. One of the most significant degenerative diseases with epidemiological implications is age-related macular degeneration (AMD), which is the leading cause of central vision loss in developed countries [10]. In the pathogenesis of AMD, chronic oxidative stress and depletion of the body's natural defenses are considered to be among the key risk factors. Of particular importance is the progressive deposition of toxic metabolic compounds in the cells of the retinal pigment epithelium (RPE), including pyridinium bis-retinoid (A2E) and lipofuscin [11, 12]. The photo-oxidation of A2E results in the formation of oxygen free radicals, which damage the retinal pigment epithelium (RPE). Previous epidemiological studies have found a significant reduction in the risk of AMD progression with increased intake of antioxidants (vitamins, micronutrients), lutein [13], omega-3 polyunsaturated fatty acids [14], and a Mediterranean diet [15]. *The Age-Related Eye Disease Study* (AREDS) demonstrated that vitamins C, E, and β-carotene combined with copper reduced the 5-year risk of developing advanced AMD by over 20% [14]. In addition, lutein or zeaxanthin, the natural macular pigments, may enhance the beneficial effects of the combination of vitamins and micronutrients used in AREDS [16]. Cardiovascular disease and AMD share several modifiable risk factors, including smoking, which increases oxidative stress; a diet high in fat and calories; and low levels of physical activity. Studies have demonstrated that patients with AMD have a higher risk of cardiovascular disease than the general population of the same age [16, 17]. Resveratrol, which is a polyphenol, has emerged as a subject of investigation for its potential to mitigate retinal oxidative stress. Experimental studies have found that A2E leads to RPE cell

damage (ARPE-19 line) [18]. Alaimo et al. demonstrated that resveratrol at a concentration of 25 μM can mitigate the cytotoxicity and typical morphological features of apoptosis observed in A2E-loaded ARPE-19 cells. The authors reported increased intercellular integrity and sealing of intercellular connections. Resveratrol has the potential to restore the intracellular balance between oxidation and reduction reactions. It also prevents A2E-induced fragmentation of the mitochondrial network. The data obtained support the thesis that resveratrol is a biological compound that can be used for therapeutic intervention in oxidative stress-related eye diseases such as AMD.

Kang et al. demonstrated that resveratrol reduced the intracellular accumulation and A2E photooxidation. These observations suggest that resveratrol and its analogs may be beneficial in the AMD treatment [19]. Lee et al. hypothesized that polyphenolic components of *Vaccinium uliginosum* L. extract protect retinal pigment epithelium (RPE) from blue light-induced damage [20]. To test this hypothesis, they exposed ARPE-19 cell cultures with accumulated A2E to blue light after treatment with *Vaccinium uliginosum* L. extract containing polyphenols. The researchers noted a significant reduction in A2E-photo-oxidation-induced RPE cell death and inhibition of intracellular A2E accumulation. Furthermore, female mice after prior exposure to the polyphenol extract for 2 weeks were exposed to 10,000 lux of blue light for retinal damage for 1 h/daily. One week after the final blue light exposure, the thickness of the outer nuclear layer and the number of nuclei were improved. Histologic examination of murine photoreceptor cells showed that the polyphenol extract had a protective effect and inhibited morphological changes in retinal layers [20]. The results of the study indicate that polyphenols are a potential source of bioactive compounds for AMD therapy.

RESVERATROL IN THE TREATMENT OF WET AMD

Studies suggest that resveratrol and fatty acids have cytoprotective effects at the level of RPE cells, so they may be beneficial in wet AMD (wAMD) [21, 22]. In RPE cells, they contribute to inhibition of oxidation and apoptosis, as well as suppression of vascular endothelial growth factor (VEGF) expression [23]. Accordingly, it can be hypothesized that oral dietary supplements containing resveratrol and omega fatty acids may help reduce the neovascularization activity accompanying wAMD, thereby effectively stabilizing and treating the degeneration [24]. Resvega® (Laboratoires Thea®/ Clermont-Ferrand, France) is a dietary supplement containing 30 mg of resveratrol, 665 mg of omega-3 fatty acids, 10 mg of lutein, 2 mg of crystalline zeaxanthin, 120 mg of vitamin C, 30 mg of vitamin E, 5 μg of vitamin D, 12.5 mg of zinc, and 1,000 μg of copper. It has been demonstrated that the daily oral intake of Resvega® capsules, in the absence of concomitant anti-VEGF intravitreal injections, can improve retinal structure and stabilize visual acuity in patients with wAMD [25, 26]. In light of the aforementioned data, we designed a one-year evaluation of the results of Resvega® supplementation in combination with aflibercept intravitreal injections in patients with wAMD. The comparison group consisted of patients treated with aflibercept in monotherapy [27]. A total of 50 previously untreated patients were randomly assigned to one of two groups, each comprising 25 patients. All study participants received three saturating doses of 2 mg aflibercept, and subsequent treatment was continued with pro re nata regimen. In one of the study groups, patients additionally received two tablets per day of Resvega supplement. Prior to treatment, each participant underwent a complete ophthalmological examination, including best corrected visual acuity (BCVA) and contrast sensitivity, optical coherence tomography (OCT), fundus autofluorescence, fluorescein angiography, indocyanine angiography, and optical coherence tomography angiography (OCTA). To assess quality of life (QoL), all participants completed the Hospital Anxiety and Depression Scale (HADS) questionnaire. No significant differences between the groups in terms of baseline demographic and clinical data were reported. At 12 months, a comparable number of aflibercept intravitreal injections were administered to both subgroups (4.52 ±1.00 vs. 4.28 ±0.90; p = 0.38). Furthermore, other clinical data did not exhibit a significant difference after the study period. The results of the questionnaire indicated that patients who took a daily supplement of resveratrol exhibited a statistically significant reduction in the incidence of depression or feelings of anxiety. Additionally, there was a statistically significant difference in the mean change in contrast sensitivity from baseline (0.17 ± 0.19 vs. 0.35 ± 0.24; p = 0.005) in favor of patients treated with the resveratrol supplement. The authors concluded that oral supplementation with resveratrol as adjuvant therapy improves quality of life in patients with wAMD who have higher rates of psychiatric disorders, including anxiety and depression, than the general population of a similar age [28]. This may be caused by the disease itself or by the treatment regimen that involves repeated intravitreal anti-VEGF injections contributing to patient's higher mental and emotional stress [29]. Moore et al. conducted research in animal models to investigate the mechanisms by which resveratrol reduces depressive behavior [30]. A total of 22 studies met the criteria for inclusion in the literature review. Behavioral aspects of depression were studied by assessing the regulation of the hypothalamic-pituitary-adrenal axis, the severity of inflammation, the concentration of brain-derived neurotrophic factor (BDNF), and the severity of neurogenesis. Based on the analysis of selected studies, resveratrol may be considered an effective treatment for depression in animal models at between 10–80 mg/kg/day, although higher doses had the most significant effects.

Future studies should evaluate the effects of resveratrol on depression in humans to determine resveratrol as a natural antidepressant with limited side effects [31].

The cases of spontaneous disease remission suggest that the human retina has a strong regenerative capacity even at advanced ages. Richer et al. administered resveratrol to three patients with progression of macular degenerative disease despite AREDS 2 supplementation [25]. These patients refused intravitreal anti-VEGF injections or did not respond to treatment with Lucentis®, Avastin® or Eylea®. The researchers observed a rapid, transient morphological effect following anti-VEGF therapy, including anatomical restoration of the retinal structure with features of improved blood flow in the choroid. The improvement in visual function reflected an anatomically visible effect. The treatment results lasted for a year or even longer when resveratrol was taken daily. The authors of the study observed unexpected systemic benefits from the effects of resveratrol. They concluded that the failure of conventional treatment should prompt the use of resveratrol as adjuvant therapy in wAMD to improve RPE function. Moreover, they suggested using resveratrol for humanitarian reasons in developing countries with insufficient medical care and poor economic performance.

Richer et al. described the effects of resveratrol supplementation in three patients with polypoidal choroidal vasculopathy, which is a subtype of wAMD, at a 2–3-year follow-up [26]. The authors used fundus autofluorescence and choroid imaging using spectral optical tomography. They also evaluated the volume of macular pigment. Visual function was evaluated using measures of visual acuity (Snellen eye chart), contrast sensitivity, and a glare test. Following the chronic inclusion of resveratrol supplementation, bilateral morphological and functional improvements were observed, in contrast to the natural aging process and disease progression. No adverse effects were observed. The authors concluded that resveratrol, when administered over an extended period of time, can stabilize the retina in patients with AMD who have undergone other therapies without success.

RESVERATROL IN THE TREATMENT OF DIABETIC MACULAR EDEMA

Oxidative stress is also a significant contributor to the pathogenesis of diabetic macular edema (DME) [32]. The efficacy and safety of vitamin supplements, including resveratrol, were investigated in patients with DME treated with anti-VEGF intravitreal injections. In a prospective study by Chatziralli et al. [33], 45 patients with DME were treated with intravitreal anti-VEGF injections (n = 23, group I) as monotherapy or in combination with a dietary supplement containing resveratrol (Resvega) (n = 22, group II). Visual acuity (VA), slit-lamp examination and spectral domain optical coherence tomography (SD-OCT) were performed in all patients at the baseline and 1 month after the anti-VEGF saturation phase, according to the PRN protocol. Both groups demonstrated a significant improvement in visual acuity at the 12-month follow-up compared to baseline, with no significant difference in mean change ($p = 0.183$). In both groups, there was a statistically significant reduction in central retinal thickness at the 12-month follow-up compared to baseline, with a significantly greater reduction observed in the group receiving resveratrol. The mean number of intravitreal anti-VEGF injections was found to be significantly lower in Group II (6.45 ± 1.12 vs. 7.39 ± 1.31 in Group I; $p = 0.018$). A vitamin supplement with resveratrol (Resvega) was found to be an effective adjunct to intravitreal anti-VEGF injections in patients with DME. The results of this study demonstrated that supplementing resveratrol had a beneficial effect on retinal morphology and a reduction in the number of drug administrations at the 12-month follow-up.

CONCLUSIONS

A review of the current literature reveals that resveratrol and dietary supplements containing resveratrol play an important role in reducing the development and progression of oxidative stress disorders. These conditions are typically epidemiologically significant and are associated with aging. Research shows that resveratrol can be used for systemic treatment. In ophthalmology, however, resveratrol is used primarily to treat degenerative retinal diseases and metabolic diseases complications caused by oxidative stress. The findings of the studies indicate that resveratrol may exert a notable effect on AMD development and progression. However, further research is needed to determine the effect of antioxidants, including resveratrol, on retinal morphology, quality of life, and mental condition in ophthalmic patients undergoing chronic treatment.

CORRESPONDENCE
assist. prof. Małgorzata Figurska, MD, PhD
Department of Ophthalmology, Military Institute of Medicine – National Research Institute in Warsaw
04-141 Warszawa, ul. Szaserów 128
e-mail: mfigurska@wim.mil.pl

ORCID
Małgorzata Figurska – ID – http://orcid.org/0000-0002-6366-802X

References

1. Pop R, Daescu A, Rugina D et al. Resveratrol: its path from isolation to therapeutic action in eye diseases. Antioxidants. 2022; 11(12): 2447;
2. Nashine S, Nesburn AB, Kuppermann BD et al. Role of resveratrol in transmitochondrial AMD RPE cells. Nutrients. 2020; 12(1): 159.
3. Bhattarai N, Korhonen E, Toppila M et al. Resvega alleviates hydroquinone-induced oxidative stress in ARPE-19 cells. Int J Mol Sci. 2020; 21(6): 2066. http://doi.org/10.3390/ijms21062066.
4. Zhou DD, Luo M, Huang SY et al. Effects and Mechanisms of Resveratrol on Aging and Age-Related Diseases. Oxid Med Cell Longev. 2021; 2021: 9932218. http://doi.org/10.1155/2021/9932218.
5. Kou X, Chen N. Resveratrol as a Natural Autophagy Regulator for Prevention and Treatment of Alzheimer's Disease. Nutrients. 2017; 9(9): 927. http://doi.org/10.3390/nu9090927.
6. Zhao YN, Li WF, Li F et al. Resveratrol improves learning and memory in normally aged mice through microRNA-CREB pathway. Biochem Biophys Res Commun. 2013; 435(4): 597-602. http://doi.org/10.1016/j.bbrc.2013.05.025.
7. Bonnefont-Rousselot D. Resveratrol and Cardiovascular Diseases. Nutrient. 2016; 8(5): 250. http://doi.org/10.3390/nu8050250.
8. Le Clanche S, Cheminel T, Rannou F et al. Use of Resveratrol Self-Emulsifying Systems in T/C28a2 Cell Line as Beneficial Effectors in Cellular Uptake and Protection Against Oxidative Stress-Mediated Death Front. Pharmacol. 2018; 9: 538. http://doi.org/10.3389/fphar.2018.00538.
9. Brown RB. Phospholipid packing defects and oxysterols in atherosclerosis: Dietary prevention and the French paradox Biochimie. 2019; 167: 145-51. http://doi.org/10.1016/j.biochi.2019.09.020.
10. Fleckenstein M, Keenan TDL, Guymer RH et al. Age-related macular degeneration. Nat Rev Dis Primers. 2021; 7(1): 31. http://doi.org/10.1038/s41572-021-00265-2.
11. Arunkumar R, Bernstein PS. Macular Pigment Carotenoids and Bisretinoid A2E. Adv Exp Med Biol. 2023; 1415: 15-20. http://doi.org/10.1007/978-3-031-27681-1.
12. Crouch RK, Koutalos Y, Kono M et al. A2E and Lipofuscin. Prog Mol Biol Transl Sci. 2015; 134: 449-63. http://doi.org/10.1016/bs.pmbts.2015.06.005.
13. Agron E, Mares J, Clemons TE et al. Dietary Nutrient Intake and Progression to Late Age-Related Macular Degeneration in the Age--Related Eye Disease Studies 1 and 2. Ophthalmology. 2021; 128(3): 425-42.
14. Van Leeuwe EM, Emri E, Merle BMJ et al. A new perspective on lipid research in age-related macular degeneration. Prog Retin Eye Res. 2018; 67: 56-86.
15. Merle BM, Silver RE, Rosner B et al. Adherence to a Mediterranean diet, genetic susceptibility, and progression to advanced macular degeneration: a prospective cohort study. Am J Clin Nutr. 2015; 102(5): 1196-206. http://doi.org/10.3945/ajcn.115.111047.
16. Chew EY. Nutrition effects on ocular diseases in the aging eye. Invest Ophthalmol Vis Sci. 2013; 54(14): ORSF42-7. http://doi.org/10.1167/iovs13-12914.
17. Mauschitz MM, Finger RP. Age-Related Macular Degeneration and Cardiovascular Diseases: Revisiting the Common Soil Theory. Asia Pac J Ophthalmol (Phila). 2022; 11(2): 94-9. http://doi.org/10.1097/APO.0000000000000496.
18. Alaimo A, Di Santo MC, Domínguez Rubio AP et al. Toxic effects of A2E in human ARPE-19 cells were prevented by resveratrol: a potential nutritional bioactive for age-related macular degeneration treatment. Arch Toxicol. 2020; 94(2): 553-72. http://doi.org/10.1007/s00204-019-02637-w.
19. Kang JH, Choung SY. Protective effects of resveratrol and its analogs on age-related macular degeneration in vitro. Arch Pharm Res. 2016; 39(12): 1703-15. http://doi.org/10.1007/s12272-016-0839-0.
20. Lee BL, Kang JH, Kim HM et al. Polyphenol-enriched Vaccinium uliginosum L. fractions reduce retinal damage induced by blue light in A2E-laden ARPE19 cell cultures and mice. Nutr Res. 2016; 36(12): 1402-14. http://doi.org/10.1016/j.nutres.2016.11.008.

21. Courtaut F, Aires V, Acar N et al. RESVEGA, a nutraceutical omega-3/resveratrol supplementation, reduces angiogenesis in a preclinical mouse model of choroidal neovascularization. Int J Mol Sci. 2021; 22(20): 11023.
22. Bhattarai N, Korhonen E, Toppila M et al. Resvega alleviates hydroquinone-induced oxidative stress in ARPE-19 cells. Int J Mol Sci. 2020; 21(6): 2066. http://doi.org/10.3390/ijms21062066.
23. Koskela A, Reinisalo M, Petrovski G et al. Nutraceutical with resveratrol and omega-3 fatty acids induces autophagy in ARPE-19 cells. Nutrients. 2016; 8(5): 284. http://doi.org/10.3390/nu8050284.
24. Berman AY, Motechin RA, Wiesenfeld MY et al. The therapeutic potential of resveratrol: a review of clinical trials. Npj Precis Oncol. 2017; 1: 35. http://doi.org/10.1038/s41698-017-0038-6.
25. Richer S, Stiles W, Ulanski L et al. Observation of human retinal remodeling in octogenarians with a resveratrol based nutritional supplement. Nutrients. 2013; 5(6): 1989-2005.
26. Richer S, Patel S, Sockanathan S et al. Resveratrol based oral nutritional supplement produces long-term beneficial effects on structure and visual function in human patients. Nutrients. 2014; 6(10): 4404-20.
27. Datseris I, Bouratzis N, Kotronis C et al. One-year outcomes of resveratrol supplement with aflibercept versus aflibercept monotherapy in wet age-related macular degeneration. Int J Ophthalmol. 2023; 16(9): 1496-1502. http://doi.org/10.18240/ijo.2023.09.17.
28. Casten RJ, Rovner BW. Update on depression and age-related macular degeneration. Curr Opin Ophthalmol. 2013; 24(3): 239-43.
29. Senra H, Ali Z, Balaskas K et al. Psychological impact of anti-VEGF treatments for wet macular degeneration – a review. Graefes Arch Clin Exp Ophthalmol. 2016; 254(10): 1873-80.
30. Moore A, Beidler J, Hong MY. Resveratrol and depression in animal models: a systematic review of the biological mechanisms. Molecules. 2018; 23(9): 2197. http://doi.org/10.3390/molecules23092197.
31. Ge JF, Xu YY, Qin G et al. Resveratrol ameliorates the anxiety- and depression-like behavior of subclinical hypothyroidism rat: possible involvement of the HPT axis, HPA axis, and Wnt/β-catenin pathway. Front Endocrinol (Lausanne). 2016; 7: 44. http://doi.org/10.3389/fendo.2016.00044.
32. Zhang J, Zhang J, Zhang C et al. Diabetic Macular Edema: Current Understanding, Molecular Mechanisms and Therapeutic Implications. Cells. 2022; 11(21): 3362. http://doi.org/10.3390/cells11213362.
33. Chatziralli I, Dimitriou E, Chatzirallis A et al. Efficacy and safety of vitamin supplements with resveratrol in diabetic macular edema: Long-term results of a comparative study. Eur J Ophthalmol. 2022; 32(5): 2735-9. http://doi.org/10.1177/11206721211057682.

Conflict of interest:
None.

Financial support:
None.

Ethics:
The content presented in the article complies with the principles of the Helsinki Declaration, EU directives and harmonized requirements for biomedical journals.