Chapter

Nutraceutical Approach for the Treatment of Retinal Inflammation after Infections

Ilaria Piano, Francesca Corsi and Claudia Gargini

Abstract

This chapter described the ability of Zika virus, a hemostat-borne flavivirus, to infect retinal pigment epithelium cells and to generate chronic inflammation capable of generating permanent damage in the host that can progress eventually to the onset of pathology related to retinal degeneration. In addition, given the lack of an effective vaccine against ZIRK, the possibility of using as a therapeutic strategy the reduction of inflammatory processes that are established as a result of viral infection through the use of bioactive phytonutrients was analyzed.

Keywords: retinal degeneration, RPE cells, Zika virus, inflammation, phytonutrients

1. Introduction

Age-related macular degeneration (AMD) is an idiopathic degenerative disease of the retina and the cause of irreversible and profound vision loss in people older than 60 years [1]. Because of the rapidly aging population, it is easy to predict a worldwide increase in the incidence of AMD, resulting in increased costs on healthcare services. AMD presents in two main forms: Dry-AMD and Wet-AMD. Dry-AMD is characterized by atrophy of retinal pigment epithelial (RPE) cells and degeneration of adjacent photoreceptors. This form of the disease accounts for approximately 25% of cases, and patients experience severe loss of central vision. In contrast, wet-AMD is characterized by the formation at the level of the choroid of new vessels (CNVs) that branch out to the outer layers of Bruch's membrane, located beneath the basal membrane of the RPE, or across the RPE into the subretinal space. These vessels are usually constituted by a fragile endothelium and therefore subject to injury with subsequent hemorrhage and macular neuroretinal detachment. This form accounts for 75% of cases with severe central vision loss [2]. Despite their different pathophysiology and symptomatology, the two forms of AMD share similar risk factors for their development.

AMD is an aging-related syndrome caused by multiple factors including environmental, nutritional, and behavioral [3, 4] as well as genetic background can make an individual more or less susceptible to these factors [4, 5]. As in most diseases affecting the outer retina, loss of visual function in AMD results from degeneration and death of photoreceptors in the central retina, but in the initial pathogenesis of dry

AMD, the involvement of RPE cells [6] has been studied. The specific genetic and biochemical mechanisms responsible for RPE degeneration in AMD are still under investigation, but recent advances in understanding dry AMD suggest that oxidative stress and inflammation may be two of the cellular mechanisms underlying RPE cell death with an important role in drusen biogenesis and perhaps in the etiology of AMD in general [7, 8].

The RPE is a monolayer of cuboidal cells subjacent to the neural retina [9]. The basal cell membrane of the RPE is in contact with Bruch's membrane, a multilayered matrix that separates the RPE from the underlying choroidal vasculature. The apical membrane of the RPE is intimately interdigitated to the outer segments of the underlying photoreceptors. The main function of the RPE, which forms a part of the blood-retinal barrier, is to support the survival and normal function of the photoreceptors, in fact it controls the exchange of nutrients, waste products, ions, and gases between the choroidal blood vessels and the photoreceptors [10]; RPE is involved in the transport of retinol necessary for the synthesis of the visual pigment of photoreceptors [11] and in the phagocytosis of photoreceptor outer segment membrane disks (POS) [12]. In addition, RPE cells produce trophic and immunological factors necessary for the survival and protection of photoreceptors and the entire eye [13].

In addition to oxidative stress and inflammation, triggered by multifactorial events, infection by pathogens may also be a cause of damage and degeneration of RPE cells [14] and eventually lead to the onset of AMD.

2. Viral infections that induce eye damage

In the last decade, the World Health Organization (WHO) has identified a list of infectious diseases that have the potential to evolve into epidemics resulting in health emergencies and increased economic pressure on healthcare systems worldwide. Moreover, for the viral infections included in the list, there are no effective preventive or curative countermeasures to date. Among the diseases included in the list were coronaviruses, responsible for the pandemic that exploded in 2020, Crimean-Congo hemorrhagic fever, Filovirus diseases (Marburg hemorrhagic fever and EVD), Lassa Fever, Nipah virus infection, Rift Valley fever, and Zika virus [15].

2.1 Ocular complications from coronavirus infections

Coronaviruses include a family of viruses capable of infecting humans discovered for the first time in 1969; the transmission of the virus occurs mainly through respiratory droplets that in contact with the mucous membranes allow the virus to penetrate in the cells. There are seven coronaviruses that infect humans, and in 2002, the virus, named SARS-CoV-1, was isolated that mainly caused benign and mild infections of the upper respiratory tract [https://www.who.int]. Then in 2012, another virus causing respiratory syndrome named MERS-CoV was isolated in the Middle East [16]. The recent pandemic of Coronavirus-19 (COVID-19) due to SARS-CoV-2, which began in December 2019, has resulted in over 108 million cases and 2.3 million deaths. These highly transmissible pathogens cause lower respiratory tract infections that can rapidly progress to severe pneumonia with an estimated mortality rate of <1% for those aged 20–54 years, 1–5% in those aged 55–64 years, and 3–11% in individuals aged 65–84 years [17]. Unlike the other two diseases, COVID-19 symptomatology varies significantly between individuals. Indeed, while many patients develop respiratory

distress and fever, cough, and fatigue, some patients may have no respiratory symptoms at onset and present with extra pulmonary manifestations, including headache, diarrhea, and vomiting.

Ocular complications have not been reported in association with SARS-CoV-1 or MERS-CoV. However, a study of healthcare workers with SARS-CoV showed that three of 36 patients (8%) had traces of SARS-CoV RNA in their tear fluid [18]. Ocular involvement was reported to a greater extent in association with COVID-19. The most common ocular manifestation is conjunctivitis with disease prevalence ranging from 2% to 32% [19]. In addition, several studies have found the presence of viral RNA in lachrymal fluid such that there is a risk of transmission through the tear film [20]. Retinal manifestations have been described through imaging studies. In a study of retinal changes in 12 adults with COVID-19, all patients showed hyperreflective lesions at the level of ganglion cells and inner plexiform layers on OCT, and four had cotton wool and microhemorrhages [21]. Another study showed that six of 27 (22%) of the COVID-19 positive patients with bilateral pneumonia showed cotton wool at an average of 43 days after the onset of COVID-19 symptoms [22].

In addition, the development of optic neuritis, disc edema, vascular tortuosity, acute macular neuroretinopathy (AMN), retinal occlusive vasculopathy (RVO), retinal artery occlusion, intraretinal hemorrhages, cotton wool, uveitis, and endogenous endophthalmitis has been reported in patients who tested positive and had moderate to severe COVID-19 symptoms. Often these diseases affecting the retina and retinal vasculature are the subject of single-case studies so it is necessary to expand these investigations in order to test the incidence of ocular complications of COVID-19 on a large scale [23].

2.2 Zika virus

The Zika virus is a flavivirus transmitted by Aedes mosquitoes and is related to yellow fever virus, dengue virus, and West Nile virus. Flaviviruses are single-stranded RNA viruses contained in capsid and coated with pericapsid. The genome encodes for a total of 10 proteins of which seven are nonstructural and three structural including: glycoprotein E (responsible for host cell infection and antigenic determinant of antibody response), capsid protein C, and membrane protein M (**Figure 1**) [24]. Zika virus was first identified in Uganda in 1947 in macaques and then in humans as early

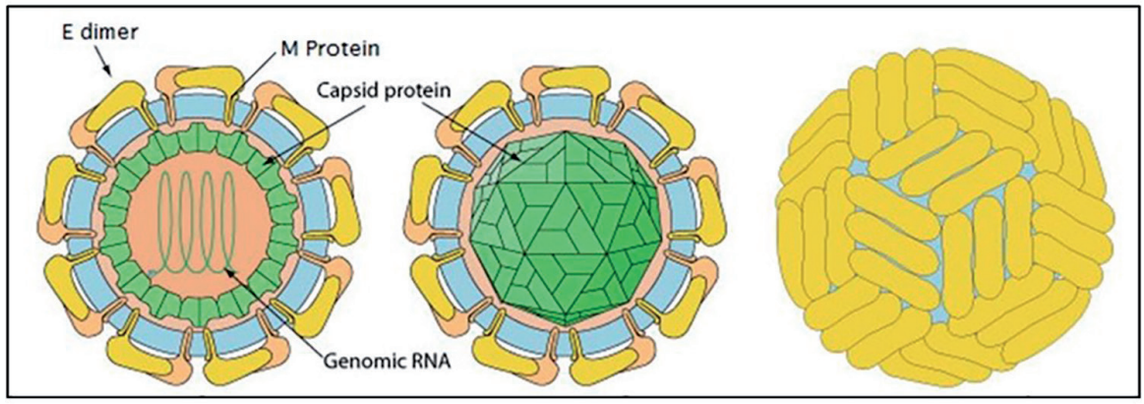

Figure 1.
Zika virus 3-D structure (Font: modified https://www.socialnews.xyz/2016/04/01/scientists-reveal-zika-virus-structure/).

as 1968. It has also been identified in French Polynesia, where an outbreak has been associated with perinatal transmission and fetal abnormalities. The virus currently present in Brazil appears to have originated from Polynesia. The clinical findings of the primary infection mimic both the dengue virus and the chikungunya virus, also present in Brazil and carried by the same mosquito. Testing for Zika virus is not readily available, making diagnosis challenging; however, serologic testing (IgM quantification) can be performed, and polymerase chain reaction (PCR) is available [25].

In adults, Zika virus infection induces symptoms such as: fever, headache, skin rash, muscle aches, diarrhea, and eye redness (**Figure 2**); but the most serious complications occur if the virus is contracted during pregnancy and especially within the first trimester. Zika virus infection, contracted in the first or second trimester of pregnancy, results in the development of microcephaly and retinal lesions in the fetus. In a study of 29 infants born to mothers who had experienced symptomalogy attributable to Zika virus, ocular abnormalities were present in 35% of the infants examined, and in seven of 10 cases they were bilateral. Characteristic lesions included posterior pole pigment deposits and areas of chorioretinal atrophy [26].

2.2.1 Ocular complications from Zika virus infections

The endemic emergence of Zika virus (ZIKV in various regions of the planet) has been accompanied by an unprecedented increase in the spectrum of ZIKV-associated diseases. It is becoming increasingly clear that ZIKV infection has implications that go beyond microcephaly, as infants born with congenital ZIKV have pathologies that also affect the eyes, ears, limbs, and possibly other organs [27]. Consequently, there has been a growing interest in understanding the pathogenesis of ZIKV in neurological diseases.

Since clinical studies have linked ZIKV to ocular abnormalities, mainly in the retina of infants and adults [28, 29] and to uveitis in children [30, 31]; for these reasons, it is important to study the pathogenesis of ZIKV in the eye to identify potential targets for therapeutic intervention since this virus currently has no effective vaccine.

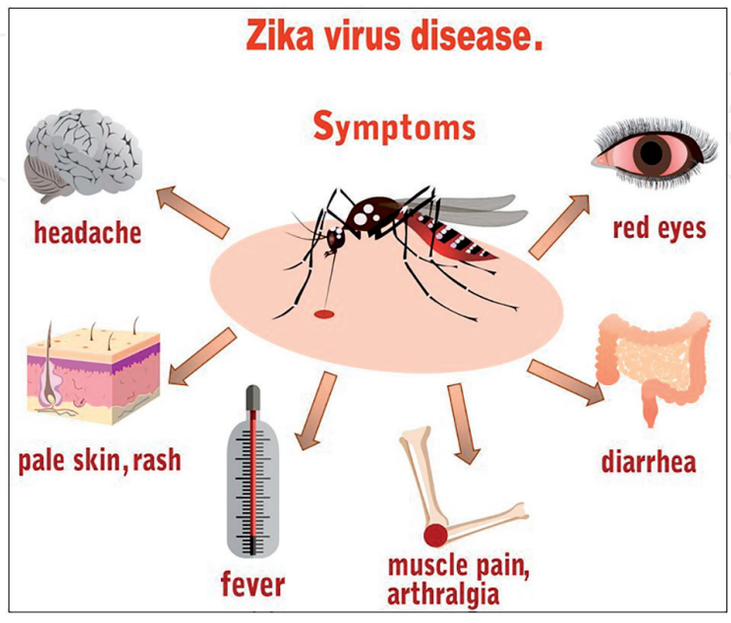

Figure 2.
Symptomatology attributable to Zika virus infection.

It has been shown that direct inoculation of ZIKV into the eye of an adult mouse causes retinal lesions with signs (chorioretinal atrophy and mottling of the RPE) that resemble of the ZIKV-associated ocular pathology described in humans. It has also been observed that ZIKV infects different retinal cell types and stimulates an innate antiviral response in the retina.

The main protective mechanism that controls the influx of innate immune cells and pathogens into the posterior segment of the eye is the presence of the blood-retinal barrier (BRB), consisting internally of retinal vascular endothelial cells and externally of RPE cells [32]. BRB dysfunction is known to allow infectious agents to enter the retina and cause inflammation and tissue damage [33].

The study by Kumar Singh and coworkers [34] shows that ZIKV has the ability to induce the expression of TLR3, RIGI, and MDA5 in RPE, HRvECs, and in the retina, suggesting that these PRRs might be involved in ZIKV recognition in the eye. Activation of PRRs leads to the production of various inflammatory mediators, including cytokines, chemokines, and IFNs both in vitro and in vivo. In this study, it was also shown that direct inoculation of ZIKV has the ability to create retinal lesions in adult WT mice, with evidence of choroidal inflammation, activation of antiviral innate immune response, and damage with atrophy and death of the RPE. The limitation of this study, in the in vivo experiments, was the intravitreal inoculation method, which itself bypasses the BRB and directly infects retinal cell types (**Figure 3**).

A further study investigated the potential mechanisms of ZIKV-induced degeneration by going to analyze retinal inflammation and endoplasmic reticulum (ER) stress in retinas at p8, a stage when the retinal tissue is still developing. The authors of this study [35] demonstrate how ZIKV-infected retinas are morphologically damaged compared with control retinas (**Figure 4**) and found that the levels of several key inflammatory molecules including chemokines (CCL2 and CXCL10), pro-inflammatory cytokines (TNFα, IL-1β, and IL-6), adhesion molecules (ICAM-1 and VCL-1), and iNOS were increased by 1.6–1300-fold in ZIKV-infected retinas. Similarly, key

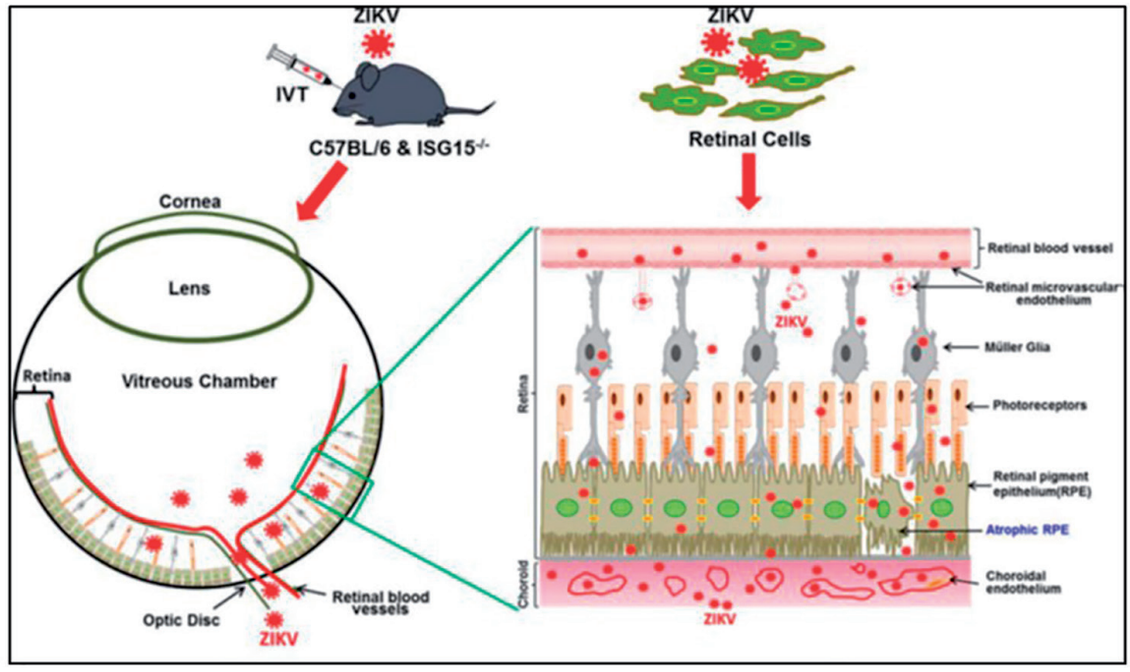

Figure 3.
Zika virus eye infection and related retinal damage. Image modified from Kumar Singh et al. [34].

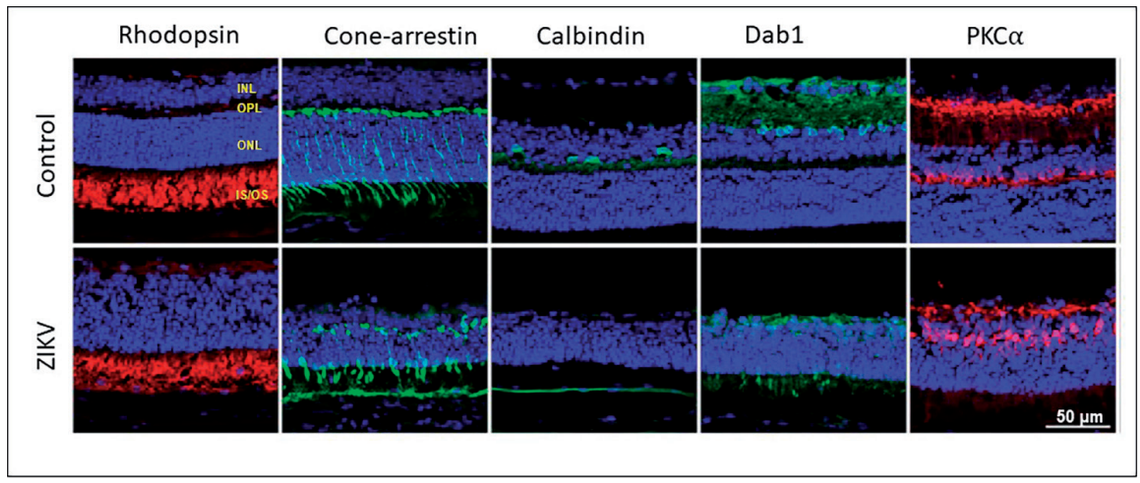

Figure 4.
Retinal degeneration induced by ZIKV infection. The image was modified from Li et al. [35].

molecules involved in ER stress, including XBP1s, GRP78, and CHOP, were significantly increased. Furthermore, in association with the increase in inflammation and ER stress, levels of cleaved caspase 3, a marker of apoptosis, and phosphorylated receptor-interacting protein 3 (pRIP3), a marker of necroptosis, were also increased in ZIKV-infected retinas. The cells most affected by this infection appeared to be localized mainly in the INL, where cleaved caspase 3-positive cells were visible, and in the IPL and GCL where pRIP3-positive cells were localized (**Figure 5**). These results

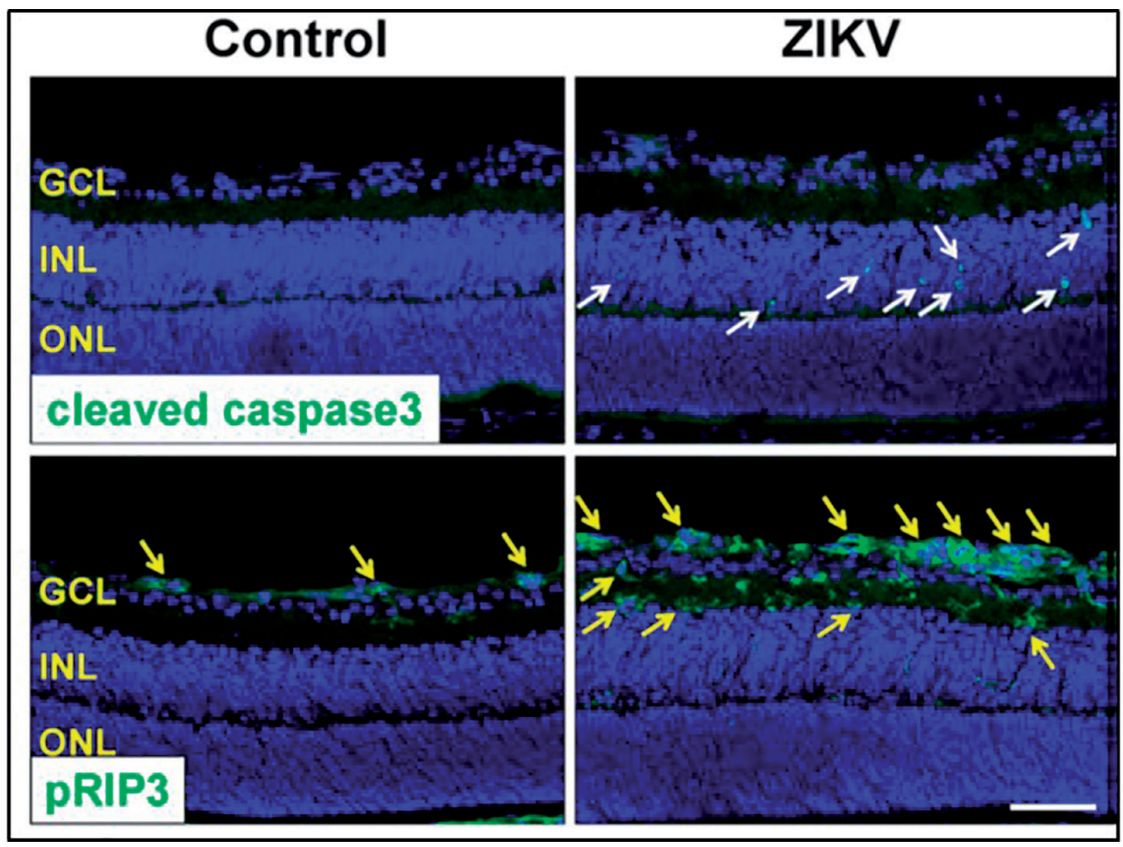

Figure 5.
Localization of key markers of apoptosis (green, cleaved caspase 3) and necroptosis (green, pRIP3) in ZIKV-infected retinas. The image was modified from Li et al. [35].

suggest that ZIKV-induced retinal degeneration may involve inflammation and ER stress by mediating cell apoptosis and necroptosis.

All of the evidence reported in the various studies concurs in suggesting that ZIKV infection leads to degeneration that can be likened to AMD-like degeneration where processes of chronic inflammation drive the progression of the disease. To date, however, it is not possible to permanently prevents this type of infection because there is no effective vaccine available, so one of the possible strategies to counteract ZIKV-induced chronic inflammation could be to use anti-inflammatory molecules. To this end, possible anti-inflammatory approaches through the use of nutraceutical molecules will be reported in the next section.

3. Phytonutrients and their applications

Natural products and their derivatives have played a significant role in medicine, generating many of the first new molecular entities (NMEs) and nearly half of all approved NMEs [36].

Scientific research is more and more focused on identifying biologically active food components that can optimize physical and mental well-being and reduce the risk of disease onset. Nutraceuticals or phytonutrients are products of natural origin, foods, or parts of them, that promote good health, longevity, and quality of life and, what is more, they can be used, in some cases, for the prevention and even treatment of chronic diseases.

Phytonutrients include the polyphenols. Polyphenols and their derivatives are widely distributed bioactive compounds in plant-derived foods (fruits, vegetables, legumes, cereals, seeds, spices, wine, tea, coffee, cocoa, and herbs) [37]. These bioactive compounds have received considerable interest over the past decade because of their wide range of biological activities. They are a broad group of compounds organic, plant secondary metabolites. The polyphenolic composition of plants is highly variable, both qualitatively and quantitatively; some of them are ubiquitous, while others are restricted to specific families or species [38]. From a structural point of view, polyphenols are compounds with one or more hydroxyl groups, associated with the aromatic ring, which can be present either in the oxidized form (quinone) or in the reduced form (phenol). Depending on the number of phenolic rings (hence the name “polyphenols") and the structural elements attached to them, polyphenols can be distinguished into flavonoids and non-flavonoids (phenolic acids, stilbenes, and lignans) [39]. Currently, about 8000 different structures of plant phenols are found. Flavonoids, in turn, are divided into six main subclasses: isoflavones, flavones, flavonols, anthocyanins, flavanones, flavanols. They are usually associated with a sugar, forming glycosides [40].

Here, in detail, we will review the activity of two polyphenols in neurodegenerative retinal diseases related to Zika virus infection.

3.1 Resveratrol

Resveratrol (3,5,4′-trihydroxy-trans-stilbene) is a plant-derived substance that is a member of the stilbenes group, non-flavonoid compounds belonging to the polyphenol family (**Figure 6**). Stilbenes are produced by the combination of the acetate and shikimate pathway.

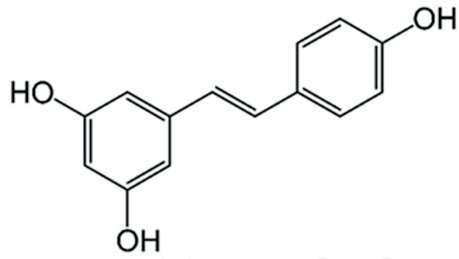

Figure 6.
Resveratrol structure.

Resveratrol is naturally found in the two isomeric forms cis and especially in the trans, which shows greater activity biological activity [41].

The most abundant dietary source of resveratrol is red grapes. Discrete amounts are also found in blueberries, berries, and the polygonum cuspidatum plant.

Resveratrol has been shown to have a powerful antioxidant action. In fact, the presence of this substance in red wine is associated with the benefits obtained by populations that habitually consume it in their diets. The cardioprotective properties of resveratrol are well known, and the presence of this compound in red wine is partly responsible for the phenomenon known as the "French Paradox." In France, habitual consumption of red wine reduces the incidence of mortality from cardiovascular disease. It is also known to have anti-inflammatory, anticancer, protective properties on nerve cells, antiaggregant, immunomodulatory, antibacterial, and antifungal properties of resveratrol. All these activities are due to the interaction of this molecule with several cellular synthetic pathways involving enzymes such as cyclooxygenase, lipoxygenase, and tyrosine kinase.

3.2 Hesperidin

Hesperidin (4′-methoxy-7-O-rutinosyl-3′,5-dihydroxyflavanone; hesperetin 7-O-rutinoside) is a naturally occurring flavanone glycoside found in citrus fruits (most notoriously oranges) and is a sugar-bound form of the flavonoid hesperitin (**Figure 7**) [42].

Flavanones, also called dihydroflavones, have a saturated C ring and can be multi-hydroxylated; in addition, several hydroxyl groups can be methylated and/or glycosylated [43].

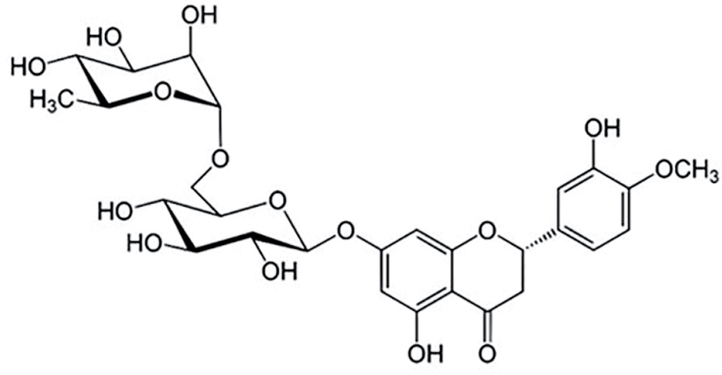

Figure 7.
Hesperidin structure.

Hesperitin is known to mediate the actions of hesperidin in the body, and since hesperidin needs to progress to the colon to be "released" by intestinal bacteria, it acts as a time release for hesperitin; one serving of hesperidin seems to increase blood levels for over the course of a day or so when consumed in this manner.

Various biological and pharmacological effects have been reported for hesperidin. It possesses the antioxidant, anti-inflammatory, and anti-carcinogenic activities [44]. Hesperidin possesses also considerable neuroprotective property in various neurodegenerative diseases, such as Alzheimer's, Parkinson's, stroke, and Huntington's [45].

4. Phytonutrients as a therapeutic perspective in the treatment of Zika-virus-induced ocular inflammation

It is well known that retinal degeneration can be induced by several factors, including genetic mutations, oxidative stress, and inflammation. Several treatments employing natural molecules, with antioxidant and/or anti-inflammatory actions, have shown efficacy in slowing the progression of retinal degeneration (e.g., AMD) [46].

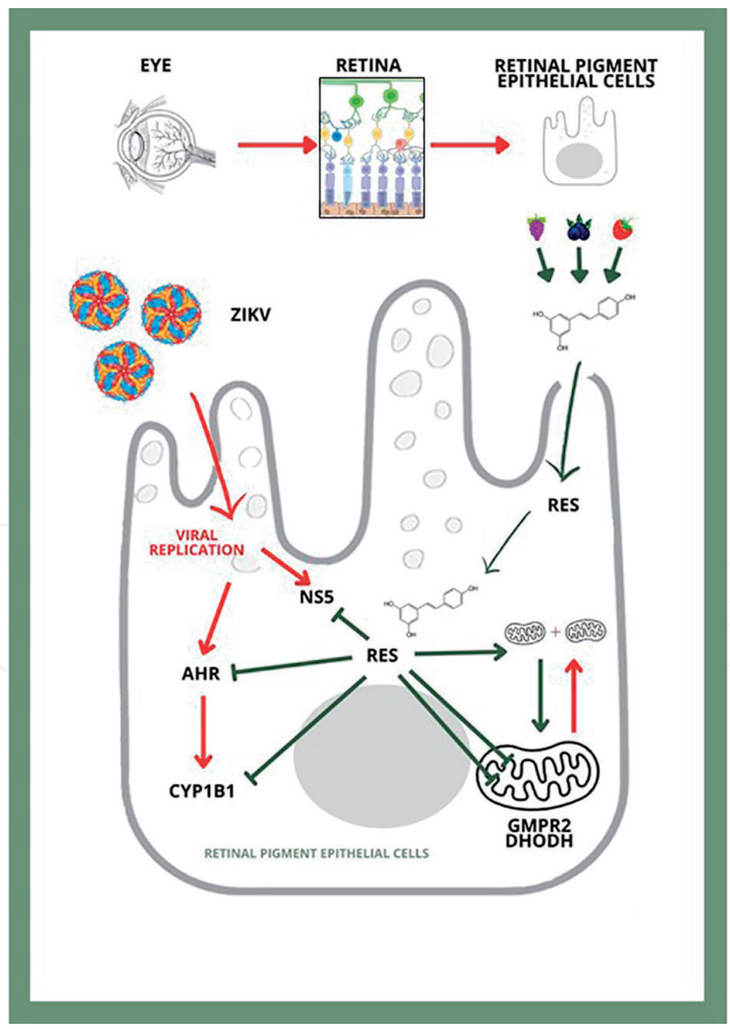

Figure 8.
Mechanism of action of resveratrol in the treatment of Zika virus retinal infection. Zika virus takes advantage of host mitochondrial enzymes for viral replication; resveratrol is able to inhibit these enzymes (GMPR2 and DHODH), effectively blocking virus replication.

Moreover, recent studies have demonstrated the antioxidant activity of Saffron, Naringenin, and Quercetin, the last are two polyphenols with known antioxidant and anti-inflammatory activities, in slowing the progression of retinal degeneration in several animal models [47, 48].

There is also a study that illustrates the efficacy of Hesperidin in protecting a retinal pigmented epithelium cell line (ARPE-19) from H_2O_2-induced damage, by inhibiting both apoptosis and ROS hyperproduction. Showing, once again, the efficacy of a polyphenol in the treatment of a retinal degeneration, such as AMD [49].

Regarding the Zika virus specifically, although the clinical manifestations at the ocular level are known, to date there is still a lack of research on the stages of the virus and consequently on potential treatments with natural molecules.

There is only one study on the efficacy of resveratrol treatment in the Zika-virus-infected ARPE-19 cell line with a focus on mitochondrial morphology.

Russo et al first showed how Zika virus infection altered the balance of mitochondrial dynamics toward the fission process in RPE cell and how these organelles lose their typical tubular shape during infection. Through a docking analysis, they study how resveratrol treatment restores the typical mitochondrial shape by acting as an inhibitor on enzymes critical for viral RNA replication (e.g., GMPR2 and DHODH). Indeed, viruses use host-specific factors to complete their multiplication cycles, and inhibition of mitochondrial enzymes involved in nucleoside biosynthesis has been shown to be an effective antiviral strategy. In conclusion, they demonstrated the efficacy of resveratrol as an antiviral agent in the treatment of Zika-virus-induced eye diseases [50]. A schematic representation of the mechanism of action of resveratrol, proposed by the authors [50], is shown in **Figure 8**.

5. Conclusion

In this chapter, we described how inflammation triggered by virus infection can lead to ocular complications capable of progressing to degenerative diseases such as AMD.

In particular, ocular complications due to COVID-19 and Zika virus have been analyzed, unfortunately this area of research is not yet well explored; especially in the former case given the recent appearance of the new virus responsible for Sars-Cov2 that is constantly evolving.

As for Zika virus, although the etiology at the level of the central nervous system and at the ocular level is known, effective therapies capable of blocking viral replication are not yet available; in fact, a specific vaccine is not yet developed.

Studies on the anti-inflammatory ability, at the ocular level and on retinal degeneration, of natural molecules have been widely resonant in the last decade; this strategy has also received interest in the treatment of Zika-virus-induced inflammation, and promising studies indicate the ability of molecules such as resveratrol and hesperetin to block the viral cell cycle. These notions, while in need of further study, open new perspectives for phytonutrient treatment of virus-induced ocular complications.

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