COVID-19 and retinal degenerative diseases: Promising link "Kaempferol"

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Abstract

Coronavirus disease (COVID-19) outbreak has caused unprecedented global disruption since 2020. Approximately 238 million people are affected worldwide where the elderly succumb to mortality. Post-COVID syndrome and its side effects have popped up with several health hazards, such as macular degeneration and vision loss. It thus necessitates better medical care and management of our dietary practices. Natural flavonoids have been included in traditional medicine and have also been used safely against COVID-19 and several other diseases. Kaempferol is an essential flavonoid that has been demonstrated to influence several vital cellular signaling pathways involved in apoptosis, angiogenesis, inflammation, and autophagy. In this review, we emphasize the plausible regulatory effects of Kaempferol on hallmarks of COVID-19 and macular degeneration.

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Introduction

COVID-19 has overwhelmed our healthcare system with an incidence of over 4.8 million death reports. Most governments implemented lockdowns, travel restrictions, and social stratification to control the pandemic. However, governments have been compelled to reopen societies because of growing economic constraints and unmet population demands. The benefits of reopening should be assessed against the risks to public health, including infection control and proper social distancing measures. This delicate balance has forced a digital shift in many businesses, allowing remote labor and ongoing services while preserving acceptable safety [1]. Nevertheless, the risks of reinfection with COVID-19 are still high with age and lifestyle disorders.

Recent research has identified diabetes mellitus and hypertension as risk factors for COVID-19 or limitations for the therapeutic potential against the disease. A disproportionate percentage of those who died were also found to be Hispanic or Black with a history of health problems such as high blood pressure, obesity, or asthma [2]. Although extra pulmonary comorbidities have gotten less attention, several studies have found connections between chronic central nervous system comorbidities and COVID-19, such as macular degeneration that causes vision loss [3].

Vision loss is primarily caused by degeneration of retinal pigment epithelial cells, which significantly affects the rods and cones where age-related macular degeneration (AMD) and diabetic retinopathy (DR) are two of the most prevalently reported, impacting about 300 million individuals worldwide [4,5]. Multiple anecdotes and published research of COVID-19 patients' eye redness and irritation suggested that conjunctivitis was an ocular symptom of severe acute respiratory syndrome coronavirus-2(SARS-CoV-2) infection at first [6]. However, the elderly are the most affected by the disease, both directly and indirectly.

Several cellular and molecular pathways in COVID-19 and associated comorbidities have been deregulated and studied for therapeutic development. The most broadly applied treatment methods for viral infections are blocking the viral entrance and replication and modulating humoral and cellular defense in the uninfected population [7]. Several drugs, including chloroquine (CQ), hydroxychloroquine (HCQ), remdesivir, favipiravir, ritonavir, lopinavir, ribavirin, dexamethasone, and arbidol, have been utilized for the treatment of COVID-19 patients. Nonetheless, these synthetic medications have several adverse effects: heart failure, permanent retinal damage from HCQ, and liver damage from remdesivir [8]. In older people, improper treatment and chronic molecular disease conditions might lead to retinal degenerative disease, and the irreversible pathogenesis necessitates the need for an alternative with minimal side effects.

Multiple in-silico analyses indicated that natural compounds derived from plants could be promising therapeutics against SARS-CoV-2 and its clinical manifestation and comorbidities [9]. Active ingredients such as flavonoids have enormous medicinal potential in regulating cell homeostasis. Kaempferol is one of the essential flavonoids extracted from vegetables, fruits, and medicinal herbs [10]. This review focuses on the plausible molecular regulation of COVID-19 and retinal degenerative disease by Kaempferol. In addition, we hope to present Kaempferol as a potential prophylactic treatment against these diseases.

The origin of COVID-19

Humans have historically been victims of deadly infectious illnesses, such as viral epidemics. SARS-CoV-2 is a novel virus that differs from SARS-CoV and MERS-CoV (Middle East respiratory syndrome coronavirus) but can cause pneumonia-like symptoms, which was first discovered in late 2019 in Wuhan, China [11,12]. Coronaviruses are non-segmented positive-sense RNA viruses that infect humans and animals primarily, causing mild respiratory and gastrointestinal diseases. Clinical studies reported that most infected people were found to have dry cough and dyspnea, as well as bilateral ground-glass opacities [13].

Hallmarks of COVID-19

The SARS-CoV-2 life cycle is a dynamic process in which the virus enters the host cell through the ACE2 (angiotensin-converting enzyme 2) receptor [14]. Once the virus is endocytosed, it is replicated by the host cells, followed by exocytosis. SARS-CoV-2 components can also bind to various cytosolic PRRs (pattern recognition receptors), resulting in damage-associated molecular patterns (DAMP) and cytokine release followed by subsequent inflammation and coagulation and activation of transcription factors including IRF3 and NFκB (Nuclear Factor Kappa B). Sepsis, multiple organ failure, and death can occur if not diagnosed and treated promptly (Figure 1) [15].

COVID-19 has been associated with several risk factors, including age, gender, environment, inherited genetic vulnerability, and pre-existing comorbidities [16]. The most severe occurrences have mostly been recorded in the elderly or those with pre-existing illnesses, mainly cardiovascular problems, including hypertension and congestive heart failure. These risk variables are strikingly comparable to the risk factors linked with MERS-CoV-related mortality (diabetes, hypertension, and obesity), even though MERS-CoV respiratory illness can affect younger people. According to current research, SARS-CoV-2 severity progressed within 14−21 days

Figure 1
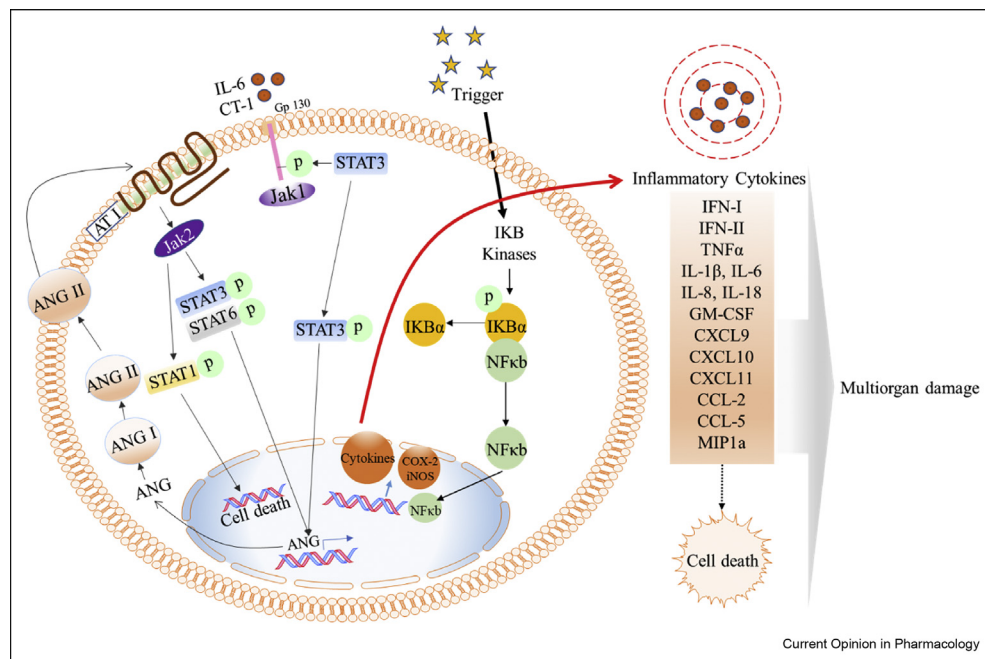
Ultimate inflammasome activation and multiorgan damage under SARS-CoV-2 infection. SAR-CoV-2 downregulates ACE2 expression which leads to the accumulation of angiotensin II and upregulation of proinflammatory mediators; green circle entitled with P represents phosphorylation; arrow represents the induction.

after infection [17]. In severe conditions, myocarditis might develop in the third week of the disease, causing irregular heartbeat that increases mortality. Recently, macular degeneration was also a risk factor for SARS-CoV-2 related mortality, which unveiled several sharing pathways involved in the disease mechanism [18].

Molecular pathogenesis of COVID-19

The ultimate causes that damage cellular macromolecules and tissues are cross-talk between oxidative stress and activation of pro-inflammatory cytokines, as seen in COVID-19 patients [19]. When SARS-CoV-2 infects a cell, it reduces the expression of the ACE2 receptor, that converts angiotensin-I to angiotensin II, further forming angiotensin 1-7, which preferentially binds to the cell surface receptor MasR (Mitochondrial Assembly Receptor), causing anti-fibrotic, anti-inflammatory, and vasodilation effects [20]. Angiotensin-II accumulates in the presence of down regulated ACE2 receptors, which bind to the cellular membrane's angiotensin II type 1 receptor (AT1R), inducing molecular hallmarks of inflammasome formation via the JAK-STAT pathway [21,22]. Since COVID-19 patients lose ACE2-mediated protection, Ang-II signaling causes clinical signs such as disseminated coagulopathy and acute tissue damage [23]. Multiple organs express ACE2 and are targets for SARS-CoV-2.

When cells continuously undergo stress and DNA damage, it activates a DNA damage repair mechanism. When the damage becomes irreversible, those cells will be programmed for cell death via the JNK pathway, which is involved in ischemia-induced cell death, reperfusion damage, and neurodegenerative diseases [24]. Initiation of inflammatory cascade occurs when TLR3, 7, 8 further upregulate the interferon type-I and type-II gene expression, and NFκB nuclear translocation which then enhances the expression of multiple pro-inflammatory genes, including pro-IL-1β, pro-IL-18, TNF-α, and IL-6 [25–27]. Cytoplasmic NLRP3 also recognizes the virus and develops the inflammasome complex with ASC and Caspase-1 (Casp-1), cleaving and releasing mature IL-1 and IL-18. These cytokines, along with TNF-α, promote phosphorylation of p38 MAPK and nuclear translocation of NFκB, which in turn secretes more pro-inflammatory cytokines and chemokines [25]. At the same time, IL-6 contributes to the cytokine release syndrome observed in COVID-19 patients [28]. Given the importance of NFκB in the mediation of cell death, which is a significant characteristic of COVID-19 pathogenesis, targeting NFκB in patients, may have therapeutic implications [29].

Another possible explanation for COVID-19's etiology is that SARS-CoV-2's intracellular replication is lethal to host cells. After SARS-CoV-2 infection, the virus multiplies by subverting the protein machinery of host cells via the ACE2 receptor in alveolar epithelial cells. The critical component proteins of the new coronavirus, the spike glycoprotein, membrane protein, and an envelope protein, are translationally integrated into the endoplasmic reticulum (ER). The increased production of nascent viral peptides may induce ER stress and UPR activation. In most individuals, host cells can tolerate ER stress caused by viral infection because of the UPR proteostasis capacity. Whereas, when the UPR is over-burdened with a load of viral protein replication, the cellular function is compromised, this eventually leads to cell death [30].

Autophagy's involvement in another set of distinct viral infections and cell types, are well-acknowledged [31]. Host autophagy has an antiviral role (also known as xenophagy or virophagy) to inhibit virus infection. At the same time, some viruses use the autophagy mechanism to aid reproduction [32]. Although the exact relationship between autophagy and CoV infection is unknown, recent evidence suggests that CoVs communicate with numerous autophagy apparatus components to promote replication of the virus where significant induction of double-membrane vesicles (DMVs) was observed [33]. DMV is an ER-derived membrane that serves as the site for forming RNA replication complexes of viruses [34]. Cells infected with SARS-CoV-2 accumulate critical metabolites and deregulate the autophagy mechanism, triggering inflammation and oxidative stress, leading to cell death across all ages [35]. Thus, the post-COVID phase must be treated with careful health monitoring and the use of appropriate nutritional supplements.

Post-COVID syndrome

Previous research has shown that SARS and MERS infections result in significant long-term neurological effects leading to several degenerative diseases such as Alzheimer's disease, multiple sclerosis (MS), Parkinson's disease, and retinal degenerative diseases via neuro-inflammation across different age groups [36–38].

Experience has demonstrated that severely sick individuals experience long-term functional impairment following discharge, which can continue for years, where old age is a known risk factor for impairment [39]. Following SARS, coronavirus infection in South East Asia in early 2003, a persistent post-viral syndrome was observed. These long-term adverse effects of SARS are similar to those experienced by patients with chronic fatigue syndrome (CFS) and fibromyalgia syndrome [40,41].

According to Hayrunnisa et al., headache is a common symptom linked with continuing SARS-CoV-2 infection (up to 34 per cent); nevertheless, headache persistence has been documented even weeks after recovery [42].

Extra cranial viral infections, stressful life events, and invasive procedures such as intubation are typical causes of new daily persistent headaches (NDPH). The pathophysiology of NDPH is unknown, but some studies believe that pain is caused by cytokine production and persistent glial activation in response to precipitating events, which is also one of the hypotheses for COVID-19 involvement in the CNS, implying a synergy between pathophysiological mechanisms [43]. Ongoing hyper inflammation and endotheliitis contribute to the disruption of the blood–brain barrier, allowing entry of innate immune cells into the brain and other pro-inflammatory cytokine cascades. Endothelial dysfunction with accompanying hyper inflammation is caused by viral down regulation of ACE2 receptors, which further promotes more damage to endothelial functionality [44–46]. No medication is advantageous in the studies conducted to date. As such, prophylactic treatment was mainly used with a tricyclic antidepressant or anticonvulsant (amitriptyline and topiramate), with varying success [47]. However, the appropriate treatment for COVID19 post-infectious inflammatory response remains unknown. Besides, following SARS-CoV-2 infection, neuro-inflammation and vascular mechanism disruption can show various ocular symptoms ranging from mild conjunctivitis to posterior ischemic optic neuropathy to bilateral para central acute middle maculopathy and acute macular neuro-retinopathy [48,49].

The global pandemic and vision loss

COVID-19 and ophthalmology have direct links and significance for hospital epidemiology, infection control, community health, and the general population, particularly the elderly. A clear–cut correlation between disease severity and retinal vein width was established, implying that this could be a non-invasive process of monitoring inflammation and endothelial dysfunction in COVID-19 patients [50]. The abnormal MRI observations in nine COVID-19 patients were also described, comprising of one or even more infarcted lesions in the macula on FLAIR-weighted images [51]. The lesions were either generated by direct inflammatory infiltration or viral-induced micro angio-pathic illness. Since the outbreak, significant studies have been performed on ocular problems, with retinal degeneration being the most important as it causes irreversible vision loss [52]. COVID-19 has also been linked to uveitis, retinovascular disease, and neuro-ophthalmic illness, according to recent research [53]. Conjunctivitis has also been reported often in COVID-19 patients [54]. The symptoms of SARS-CoV-2 infection have yet to be explained entirely.

Big data could be utilized extensively to drive the triage of ophthalmology clinic visits to study the risks of glaucoma, diabetic retinopathy, age-related macular degeneration against COVID-19 exposure [55]. Another recent epidemiological study found at the start of the pandemic in China's Hubei region, among 276 confirmed cases, the ratio of patients who wore eyeglasses was lower than the general population [56].

Retinal degenerative disease: an incurable concern

COVID-19 has forced people to stay isolated at home and minimize the availability of follow-up medication and therapeutics from the ophthalmic workstations. Due to the pandemic, the delayed ophthalmic cases have caused impaired visual function and an increased rate of scar formation in the sub-macular zone. In the non-delayed cases, visual function remained constant with favorable anatomical results, highlighting the need for regular follow-up for patients. Furthermore, appropriate hospital procedures during pandemics are critical for prompt treatment for chronic diseases [57]. Optical Coherence Tomography (OCT) revealed lesions at the inner plexiform and ganglion cell layers post SARS-CoV-2 infection [58]. Following are the significant irreversible blindness diseases that are shown to share clinical characteristics post COVID-19 disease.

Age-related macular degeneration (AMD)

AMD primarily affects the elderly group. At the same time, because of age and other co-existing illnesses, this vulnerable population is frequently at an elevated risk of COVID-19-related mortality and morbidity [59]. Furthermore, slit-lamp inspection and intra vitreal injection procedures provide a higher risk of viral transmission because of the procedures' proximity. On the other hand, permanent vision loss induced by delaying intra vitreal treatment in wet AMD might negatively affect long-term societal and economic consequences. Globally, there has been an unprecedented drop in the number of patients seeking medical attention at accident and emergency rooms, even in potentially life-threatening situations, due to fear of catching the virus [60,61]. In ophthalmology, there are reports in the literature of patients failing to keep their eye clinic appointments for sight-threatening conditions [62,63].

Among COVID-19 patients, studies discovered that more than one-fourth of those with AMD died, compared to the average mortality rate of 8.5 per cent [18]. They additionally found a significant decrease in nAMD referrals throughout the initial months of the COVID-19 outbreak and lockout. According to a conservative estimate, a three-month delay in treatment might result in substantial vision deterioration in the following months [64].

Diabetic retinopathy

Lack of physical activity and dormant working culture caused by lockdown rules may be detrimental to individuals who have blindness. In healthy adults, reducing daily steps by ten times can impair sensitivity

to insulin and impede metabolic activity, increase fat deposits, decrease muscular strength, worsen cardiovascular performance, and lead to diabetes mellitus and related ocular complications [65,66]. A recent study describes the increase in diabetic retinopathy up to fivefolds, considered a leading risk factor for unfavorable COVID-19 outcomes [67]. Further demographic analysis may uncover the influence of lockdown and the severity of diabetic retinopathy during the COVID-19 pandemic.

Glaucoma

Glaucoma, which affects an estimated 80 million people worldwide, is an irreversible illness caused by degeneration of the optic nerve responsible for transferring information from the retina to the brain [68]. It is the Western world's second-biggest cause of blindness. The COVID-19 incident has accelerated the progression of glaucoma problems in previously diagnosed patients, resulting in permanent loss of visual acuity in some instances, which is irreversible. The dread of going to a specialist's appointment, as well as the digital divide in older people's ability to communicate online with their ophthalmologist, have both contributed to this scenario [61].

Entry of telemedicine

The introduction of telemedicine made a promising entry by aiding the patients in need of medication [69]. However, exposure to infections or post-infection period, inflammatory cytokine storm holds the domination over the healing mechanism in the human body.

The proclamation of a global lockdown prompted the development of new innovative digital engagement tactics. It also digitized schooling and all other modes of communication, increasing the use of digital gadgets worldwide and resulting in the gradual degradation of eye health across all age groups [70].

Thus, it hints at the necessity of a daily nutritional supplement to help the body fight against the infection, vision loss due to infection, or the change in lifestyle in the pandemic itself.

Promising therapy using flavonoids

Several vaccine platforms entered into clinical evaluation [71]. These include nucleic acid vaccines, viral vector vaccines, inactivated virus, and antigen antibody-based vaccines. Initially, treatments for COVID-19 were restricted to those who were under clinical studies [72]. However, several vaccinations had been put forward without complete phase clinical trials due to the emergency factor. Because of the pandemic's novelty, scientists are still seeking viable vaccinations and medicines to treat the pathology. One of the most challenging concerns is reducing inflammation while preserving the patient's healthy immune response. In this case, research should concentrate not only on effective medications but also on nutrition. The significance of good nutritional status and dietary habits has been heavily highlighted in the COVID-19 epidemic, not only to avoid the appearance of non-communicable diseases (NCDs), which can result in more severe infections, but also to control the inflammatory condition of the patients. Indeed, underestimating the importance of diet in COVID-19 patients can significantly impact their prognosis [73].

Targeting ACE2 is a well-identified therapeutic strategy against COVID-19. According to recent research, the ocular surface and retina contain the essential proteins for SARS-CoV-2 infection, including trans membrane serine protease 2 (TMPRSS2), CD147, ACE2, and Cathepsin L (CTSL), which was validated through tear samples [74]. Several flavonoids were identified in-silico as potential inhibitors that target the virus's main protease (Mpro) and ACE2 receptors [75]. However, no study has been performed based on the benefit of flavonoids against COVID-19 and retinal degeneration together. Considering the age and infection, together with cytokine storm and blood–brain barrier breach in the disease condition, we suggest that Kaempferol can be a potential therapeutic intervention using natural compounds against COVID-19 and its ophthalmic manifestation, directly and independently.

Kaempferol: a potential multifunctional flavonoid against COVID-19 and retinal degenerative disease

Kaempferol (3,4′,5,7-tetrahydroxyflavone) is a flavonol widely found in several fruits and vegetables [76] of the human diet in the glycosylated or aglycone form reported to modulate many critical components in cellular signal transduction pathways related to apoptosis, angiogenesis, autophagy, inflammation, and metastasis [77–80]. Interestingly, although kaempferol tends to preserve cell viability, driving a protective effect, it also induces apoptosis by inhibiting cancer cell proliferation and angiogenesis. Here we have represented the most crucial signaling mechanisms of kaempferol in normal and disease conditions (see Figure 2).

Kaempferol ameliorates inflammasome formation

The NOD-, LRR- and pyrin domain-containing protein 3(NLRP3) is activated by a variety of events, including viral infection, via the DEAH-Box Helicase 33 (DHX33) [81,82] and is then attracted to mitochondrial antiviral signaling (MAVS) or mitofusin 2 [83], where it recruits the apoptosis-associated speck-like protein with a caspase recruitment domain (ASC) and pro-caspase-1, leads to NLRP3 inflammasome formation, caspase-1 activation and proteolytic conversion of pro-IL-1 and pro-IL-18 into its active versions and increased

Figure 2
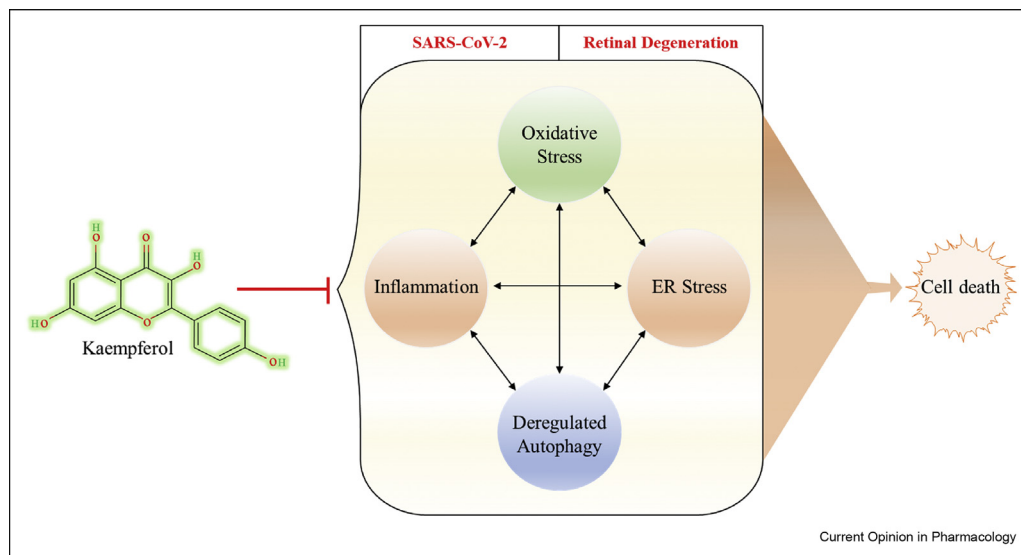
Diagrammatic abstract of kaempferol against molecular web of pathogenesis. Kaempferol — (PubChem CID5280863); ER, Endoplasmic reticulum.

secretions [84]. The NLRP3 inflammasome is constitutively expressed in various eye parts, including the retinal pigment epithelium and ONH astrocytes in both humans and mice, indicating the importance of this mediator in the ocular defence system [85,86].

In COVID-19 disease conditions, the viral protein activates NFκB, leading to the expression of NLRP3 [87], which is also seen to be activated in the presence of amyloid-β, A2E, or lipofuscin in the context of AMD [88]. NLRP3 can also be activated via the ATP-controlled P2X7 channel, reacting to reactive oxygen species buildup in the RPE [89] due to cathepsin B release from damaged lysosomes. The role of IL-18 in the RPE has yet to be entirely determined, yet the expression of this cytokine is constitutively shown in the RPE [90].

The ORF3a-TRAF3 interaction induces ASC ubiquitination, which results in caspase 1 activation and IL-1 maturation. On the other hand, ORF3a also binds to TRAF3 and activates NFκB, resulting in the transcription of the pro—IL-1 gene. NLRP3 inflammasome activation has also been observed in pre-clinical investigations of glaucoma, where increased cytokines are thought to induce neurotoxic inflammation, culminating in axon and retinal ganglion cell (RGC) degeneration [91]. As a result, NLRP3 becomes the primary focus for alleviating the inflammatory condition.

Docking studies on kaempferol showed equivalent binding affinity and docking positions on specific proteins similar to a known NFκB inhibitor (MG-132) [92]

which is then validated by *in vitro* and *in vivo* studies resulting in a significant reduction in pro-inflammatory and oxidative stress markers [93,94].

Chronic inflammation leads to neuro-inflammation and causes the onset or progression of various neurodegenerative disorders, such as inherited retinal diseases (IRDs), neo-vascular retinal disease, DR, or AMD, all of which promote retinal health degeneration by cytotoxic effects on photoreceptor cells. At the onset of each disease, there is specific damage in these degenerative retinal diseases, but studies suggest that even low-grade inflammation also could trigger disease progression [95]. Hence, kaempferol can help in maintaining cellular homeostasis by preventing inflammasome formation and cell death (Figure 3).

Kaempferol inhibits oxidative stress-induced apoptosis

The term oxidative stress (OS) refers to a disproportion between harmful reactive oxygen species (ROS) and antioxidants resulting in redox signaling tumult and irreversible oxidative damage [96]. ROS is highly linked to neurodegenerative diseases that damage the brain and associated organs due to its excessive concentration and accumulation [97]. ROS mechanisms and multiple organ insult have been studied in the pathogenesis of COVID-19 [98].

Protein 3a (U274), the most considerable accessory viral channel-forming protein with 274 amino acids, plays a vital function in the corona viral particle release phase during infection. In addition to the viral release

Figure 3
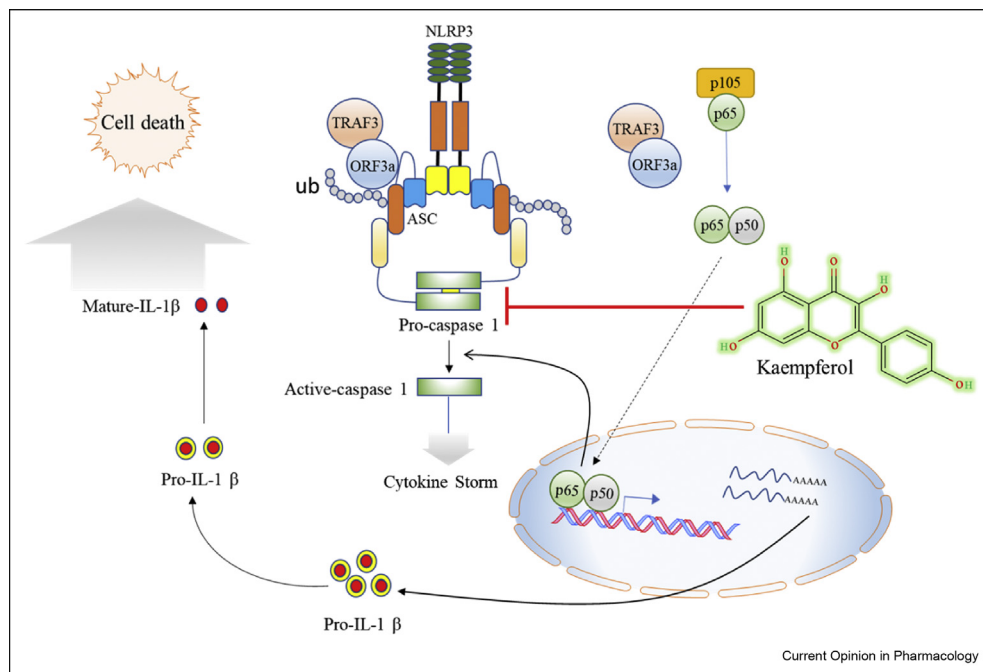
NLRP3 signalling and inflammasome formation. Kaempferol mitigates the cytokine storm by inhibiting caspase activation; Dotted arrow (Translocation into nucleus); Red --| represents the inhibition); Kaempferol- (PubChem CID5280863).

procedure, the 3a protein's role in caspase-1 activation and its consequent stimulatory effect on NLRP3 inflammasome is important in IL-1β secretion and pyroptotic death in lung cells, respectively. The 3a protein of SARS-CoV-2 was produced in Xenopus oocytes to test the inhibitory impact of kaempferol and its derivatives. However, despite considerable inhibition on 3a protein, kaempferol glycosides with more solubility showed more inhibitory solid effects [99].

On the other hand, hyperoxic insult and apoptosis have been examined in the presence of various vitamins as a rescuing factor [100]. Kaempferol protects retinal pigment epithelium cells from hydrogen peroxide-induced inflammation and apoptosis by activating SIRT1 and inhibiting PARP1, which opens up a significant gateway for more experiments and further insights [101].

VEGF is considered a critical factor that is significantly upregulated in COVID-19 and retinal degenerative disease, where OS plays a major part [102−104]. Kaempferol was proven to be effective in preventing cerebellar granule cell (CGC) death by suppressing caspase-3 activation [105], inhibition of lipofuscin formation, and also reducing angiogenic activity where VEGF is pointedly down regulated [106,107], suggesting the life-prolonging activity of the component. In a recent report, VEGF-D was identified as a COVID-19

progression biomarker [102]. Thus, the anti-oxidative regulatory activity of kaempferol could protect retinal and alveolar cells from undergoing apoptosis (Figure 4).

Kaempferol can modulate autophagy in disease conditions

Autophagy is a cellular catabolic mechanism that governs protein recycling, degradation and cell survival [108−110]. In typical cases, autophagy may counteract viral infection by promoting the survival mechanism of immune cells, but in disease conditions, viruses escape the autophagy-mediated degradation and even facilitate their replication [111]. Several autophagy-modulators exhibit antiviral therapeutic potentials. However, more studies should be conducted to come up with the specific link. DMVs imitate autophagosomes after viral infection, and these structures then merge with the lysosome and late endosome, destroying the sequestered cytoplasmic cargo [112].

Viruses can alter certain host cell mechanisms, such as metabolism, cellular trafficking, and immune responses for their survival (Figure 5) [113]. The NSP6 (Non-structural Protein 6) virus protein induces autophagosome production by promoting the production of LC3-I-coated DMVs, which are required for viral RNA transcription and replication and prevent the host cell mechanism of matured autolysosome formation [114]. Thus, finding a novel drug against

Figure 4
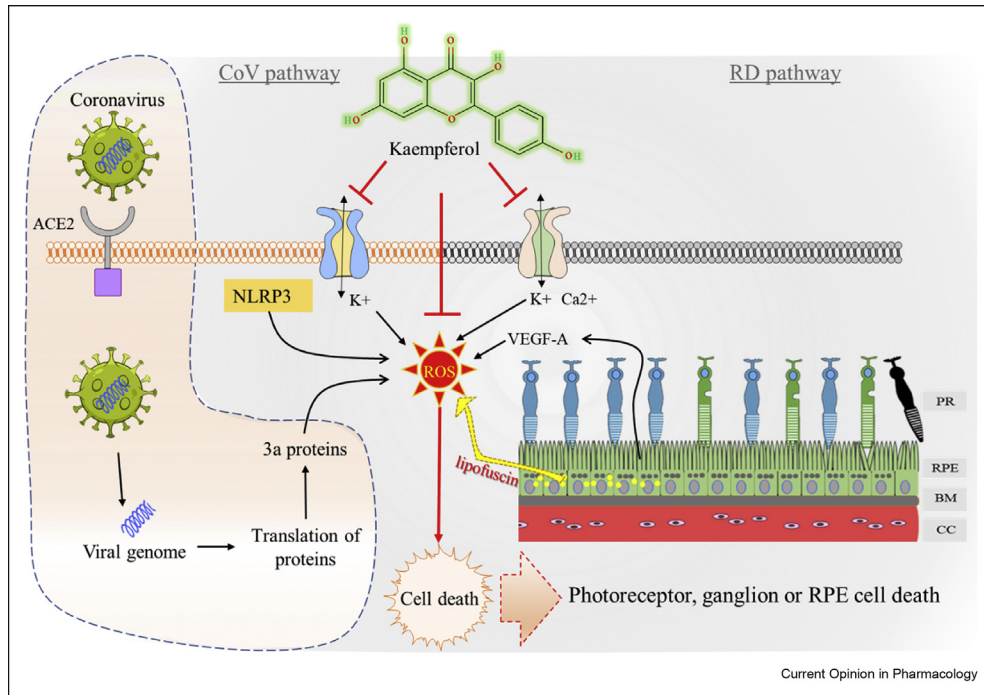
Potential benefits of kaempferol against oxidative stress in COVID-19 and retinal degeneration. Yellow spots represent the lipofuscin accumulation inside the retinal pigment epithelial cells (RPE); PR, Photoreceptors; BM, Bruch's membrane; CC, Choriocapillaris.

Figure 5
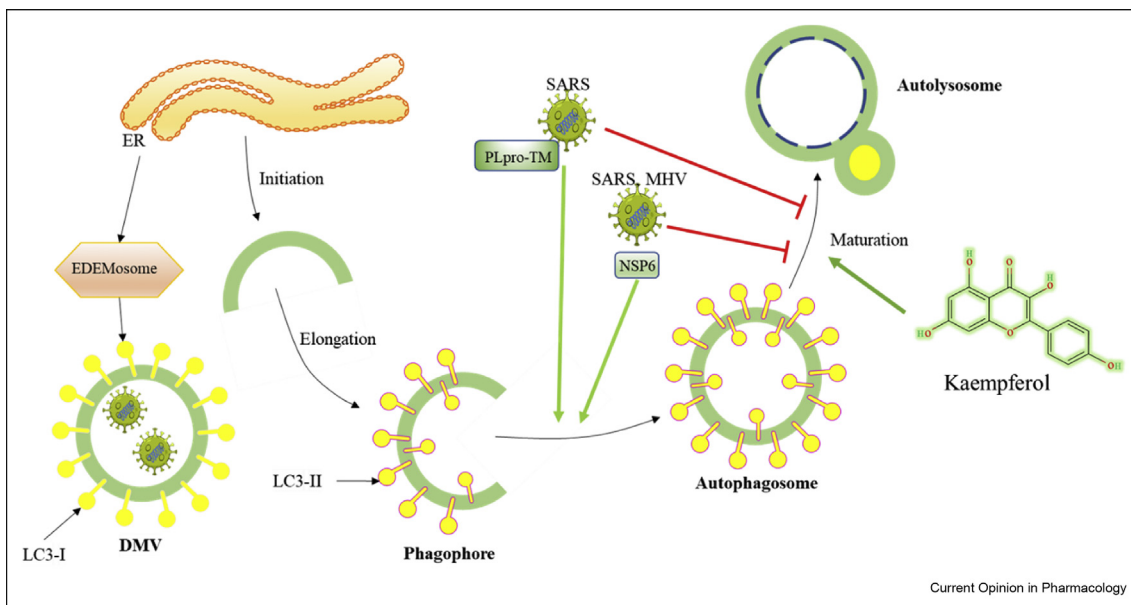
Modulation of autophagy by SARS-CoV-2. Kaempferol enhances the maturation of autophagosome to autolysosome in autophagy; DMV, Double-membrane vesicle; ER, Endoplasmic Reticulum; LC3, Microtubule-associated protein 1A/1B-light chain 3; PLpro-TM, membrane-anchored papain-like protease; NSP6, Non-structural Protein 6; Arrow shows the induction; Red --| represents the inhibition.

the deregulated autophagy pathway could combat COVID-19.

Targeting the life cycle proteins of CoVs has introduced many reactive medicines against CoVs, but safe and effective medication development is still ongoing, where CQ and its derivative HCQ as therapy has sparked debate [115]. The transcriptome analysis revealed that in SARS-CoV-2-infected Calu-3 cells, the majority of the 471 TFEB-regulated autophagy gene expressions from the coordinated lysosomal expression and regulation (CLEAR) network were down regulated [116].

Autophagy is also reported to be deregulated in retinal degenerative diseases, where lipofuscin is accumulated in the retinal cells. The photoreceptor outer segment in the eye sheds daily as a diurnal process, and in older people, the clearance of this gets disrupted and accumulates as lipofuscin, which together with A2E leads to DNA damage and cell death, which are the clinical characteristics of AMD [117–119]. Therefore, SARS-CoV-2 infection is more deleterious and can even lead to lipofuscin accumulation due to the modulation of lysosomal function in autophagy.

Kaempferol, which targets the autophagy process, causes a rise in the immuno reactive band LC3-II and a substantial increase in mature autophagosomes carrying digested material. Even at the dose of 30 μM, it could induce autophagy in neuronal cells without toxicity [120]. Kaempferol inhibits NLRP3 inflammasome activation and promotes autophagy in microglia [121]. Here we propose that kaempferol can suppress the virus replication and its activity by inducing autophagy, which could aid in the clearance of lipofuscin accumulation in enhanced autophagy (Figure 5).

Kaempferol can rescue cells from ER stress-mediated apoptosis

Apoptosis is a critical mechanism that maintains tissue homeostasis by removing damaged cells from viral infection or DNA damage caused by free radical production and restoring them to standard cellular architecture [122]. Loss of control over apoptosis can thus result in disease, with over-activation leading to loss of function and under-activation leading to disruptive events. However, it is shown that NFκb inhibitors can suppress the up-regulation of IL-1β and TNF-α in those cells [123].

Viral infection can impair ER function, causing ER stress and apoptosis by modulating the downstream critical ER stress signaling components such as ATF6, IRE1, pERK, and elF2a. Additionally, SARS-CoV-2 can activate p38 directly or via E protein, by activating syntenin, which up regulates p38 expression and thus promotes pro-

inflammatory cytokine secretion. MKK4 and MKK7 can also activate JNK, along with SARS-CoVs, N, 3a, 3b, and 7a proteins, to promote pro-inflammatory cytokines and apoptosis (Figure 6). Moreover, viral infection in the lungs reduces blood oxygen supply, resulting in hypoxia, cell death, and severe organ dysfunction [124].

UPR was recently revealed as a promising antiviral target in the battle against coronavirus. Notably, pharmacological blockage of the UPR significantly decreased viral replication [125]. The likely mechanisms underlying ER stress and the induction of the UPR response on SARS-CoV-2 infection are excessive viral protein synthesis, modification, and folding; severe ER membrane restructuring for the formation of DMVs for viral genome replication; and ER membrane depletion due to the continued virions formation and autophagy [126].

Targeting UPR signaling pathways at various phases opens up the possibility of promoting cell survival, preventing neuronal cell loss, and developing treatments for neurological disorders [127]. The sigma-1 receptor (Sig-1R) is an ER membrane-bound chaperone that functions as an initial regulator of ER stress, making it suitable for host-based repurposing approaches [128]. Several studies have also shown that IRE1 is a potential target and one of the primary signaling proteins in the ER as it is altered in COVID-19

Figure 6
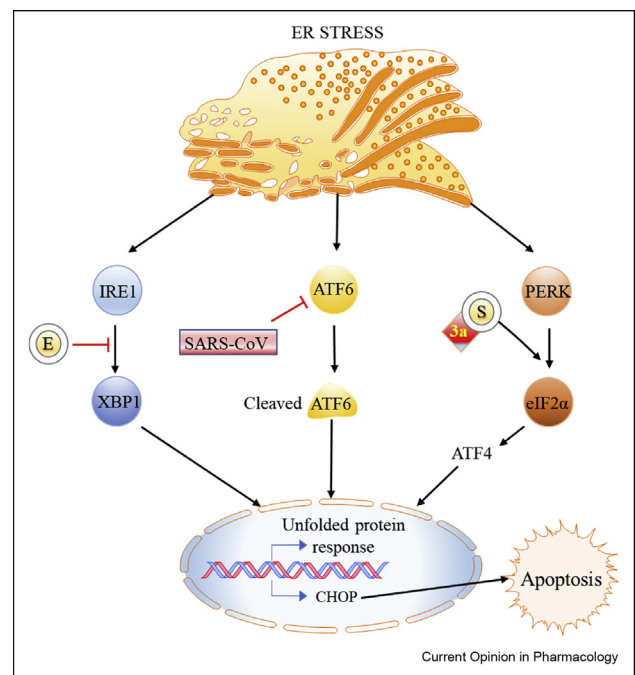
SARS-CoV-2 infection and UPR; S, SARS-CoV spike protein; E, SARS-CoV-2 envelope protein; 3a/ORF3a, SARS-CoV-2 Open Reading Frame 3a; Arrow shows the activation; Red --| represents the inhibition.

and retinal degenerative disease [129,130]. In addition, to IRD, UPR activation has been linked to other pathophysiological conditions such as glaucoma, which is caused by deterioration of retinal ganglion cells; AMD, which is caused by RPE damage; diabetic retinopathy, a neuro-vascular diabetic complication; and cataracts, which are caused by stressed lens epithelial cells [131].

Thousands of clinical trials are underway, repurposing FDA-approved drugs and assessing their safety and efficacy [132]. The discovery of small-molecule inhibitors that could target UPR machinery and lower ER stress has piqued the interest of many researchers, which led to the identification of many compounds with the ability to modulate ER stress in the past, which include TUDCA (chemical chaperones) [133], salubrinal (inhibitor of eIF2 dephosphorylation) [134], and valproate (chaperone inducer) [135], synthetic triterpenoids [136]. Moreover, multiple studies have been conducted to prevent the pro-apoptotic protein from triggering cell death, in which CHOP (C/EBP homologous protein) plays a significant role [137].

Kaempferol is a flavonoid that inhibits the production of CHOP, a pro-apoptotic transcription factor, and promotes the expression of GRP78, a transcription factor involved in ER stress-induced apoptosis. Furthermore, kaempferol inhibits ER stress by modulating the IRE1/TRAF2/JNK signalling pathway [138]. Notably, it appears that kaempferol can suppress ER stress in methods other than directly targeting it. Kaempferol has also been proven to have a neuro protective impact via reducing ER stress in neurodegenerative diseases [139] and inducing neuroblastoma differentiation by targeting IRE1α [140,141]. Considering the mentioned research, we suggest kaempferol can protect the cells from ER stress in COVID-19 and retinal degenerative disease, enhancing the survival mechanism by eliminating the accumulation of misfolded proteins and other cytotoxic factors.

Conclusion

Since developing a new drug may take many months before it reaches the public after clinical trials and research, it necessitates an alternative potential natural compound with minimal or zero side effects. Several repurposed drugs and vaccination have put many lives in uncertainty and even mortality. Vision problem was another concern that came with the COVID-19 pandemic. Either delayed treatment due to fear, lifestyle, or as an adverse effect of COVID-19 is linked with visual acuity. Some studies on the Hispanic population even revealed that patients with macular degeneration were more prone to disease and mortality. COVID-19 and its comorbidities have been immensely studied to understand its mechanism of pathogenesis, unveiling various molecular signaling pathways to target, where

COVID-19 and retinal degenerative diseases share similar mechanisms. Traditional medicines, such as flavonoids, were discovered to be beneficial in the aetiology of COVID-19 as well as retinal degenerative disease, where kaempferol has exhibited considerable neuroprotective effect, principally resulting in an overall anti-inflammatory impact. Kaempferol was also beneficial against autophagy dysregulation, ER stress, and oxidative stress. Hence, we suggest that regular dietary management with kaempferol could maintain the cellular homeostasis despite the age group to protect self from vision problems and from SARS-CoV-2 infection to a level. Further studies with kaempferol on these disease models could bring more insight into the sharing of molecular web and pathogenesis.

Conflict of interest statement
Nothing declared.

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