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Mechanisms of selected functional foods against viral infections with a view on COVID-19: Mini review

Alexander Haslberger G.[1], Ursula Jacob[2], Berit Hippe[3,4], Heidrun Karlic[5]

[1]Department for Nutritional Sciences, University of Vienna, 1090 Vienna, Austria; [2]Dayclinic Dr. Jacob, 81675, Germany; [3]HealthBioCare, Vienna, Austria; [4]Biogerontology Corp, FL 33139 USA; [5]Department of Internal Medicine I, Division of Hematology and Hemostaseology, Medical University of Vienna, 1090 Vienna, Austria

Corresponding Author: Alexander G. Haslberger, PhD, Department for Nutritional Sciences, University of Vienna, 1090 Vienna, Austria

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ABSTRACT

Following research obtained from the previous SARS and MERS outbreaks, we've gained knowledge about the mechanisms of bioactive plant ingredients against the attachment and replication of COVID-19 as well as overshooting immune responses. This could be used for designing COVID-19 trials utilizing bioactive compounds. The receptors for SARS, ACE-2, and CD26 show associations with mechanisms that regulate human senescence. Several functional foods interact with the epigenetic regulation of viral infection and mechanisms of senescence. This review concentrates on the link between bioactive plant ingredients and their activities against mechanisms of viral infections.

Keywords: COVID-19, Epigenetic, Quercetin, Curcumin, Epigallocatechin gallate, Phloretin, Berberine

INTRODUCTION

Evolution of anti-viral defence mechanisms: The fight of organisms against viral attacks has occurred since the early development of bacteria, fungi, eukaryotic cells, plants, higher organisms, and human beings. In response, bacteria developed defensive enzymes to cut up DNA or RNA from viruses, helping us to develop CRISPR/CAS systems to specifically modify DNA or RNA [1, 2]. Lower organisms began to develop innate immune systems [3, 4, 5, 6]. In the human innate immune system, three classes of receptors, designated retinoic acid-inducible gene I (RIG-I)-like receptors (RLRs), toll-like receptors (TLRs), and NOD-like receptors (NLRs). Sense viral components, such as double-stranded (ds) RNA, single-stranded RNA, and DNA, play an essential role in the production of immune responses such as type I interferons (IFNs) and proinflammatory cytokines [7, 8]. While the RLRs play essential roles in the recognition of RNA viruses in various cells, plasmacytoid dendritic cells utilize TLRs for detecting virus invasion. Higher vertebrates lately developed an adaptive immune system where several distinct DC subsets are stimulated to migrate from the site of infection (e.g. in the lungs) to the draining lymph nodes [9]. These migrant DCs have a crucial role in initiating the antivirus adaptive immune response to invading viruses. After entering the infected lungs, effector T cells that were generated in the lymph nodes undergo further modifications that are shaped by the inflammatory milieu [9]. Co-stimulatory receptor-ligand interactions between effector T cells and various cell types presenting viral antigens in the infected lungs modulate the host adaptive immune response *in situ.* Effector T cells that produce pro-inflammatory mediators are also the major producers of regulatory (anti-inflammatory) cytokines, providing a fine-tuning mechanism of self-control by effector T cells responding to viruses in the inflamed tissue [9, 10].

Mehta and colleagues postulated that a cytokine storm, a hyper inflammation seen in COVID-19 infections could be a driver of severity that is amenable to therapeutic targeting. This is represented by retrospective data which has shown that systemic inflammation including Il-6 excess is associated with adverse outcomes [11, 12]. However, it is equally plausible that increased virus burden secondary to the failure of the immune response to control infection drives inflammation and consequent severity. This has been shown for other viruses rather than augmented inflammation being an inappropriate host response that requires correction as people suffering from disturbed immune functions, viruses may augment inflammatory processes [13]. Preventive and therapeutic strategies against viral infections include the inhibition of viral attachment to host cells, inhibition of viral replication, the enhancement of immune responses against the virus, and modulation of the immune response to prevent overshooting inflammatory complications.

Virus entry: Viruses enter host cells via several mechanisms including endocytosis, macrocytosis, pinocytosis, and phagocytosis. They can also fuse at the plasma membrane and spread within the host via cell-to-cell fusion or syncytia. The respiratory tract is a major place of entry for viruses into the body. Infection of the respiratory tract can, if severe, induce life-threatening damage to the lungs. Coronavirus uses its spike glycoprotein (S) to bind its receptor. For SARS-CoV-2, the CoV spike (S) protein plays the most important role in viral attachment, fusion, and entry. The receptor-binding domain (RBD) binds strongly to human angiotensin-converting enzyme 2 (ACE2) receptors [14, 15, 16, 17, 18]. Also, the S1 domain of COVID-19's spike glycoprotein interacts with the human CD26 (also known as DPP4), a key immunoregulatory factor for hijacking and virulence [19]. CD26 is expressed both as a soluble form in plasma and on the cell surface of various immune and nonimmune cell types and is associated with inflammation [20, 21, 22]. Inhibitors of CD26, such as citrus flavonoids [23] and high fiber diets, are used therapeutically to treat patients with Type 2 diabetes mellitus (T2DM) [24, 25]. Obesity and diabetes are acknowledged as risk factors in COVID 19 infections [26]. Epigenetic dysregulation of ACE2 and interferon-regulated genes might suggest increased COVID-19 susceptibility and severity in lupus patients [27].

The S protein contains two functional domains: a receptor-binding domain and a second domain which contains sequences that mediate the fusion of viral and cell membranes. The S glycoprotein must be cleaved by cell proteases to enable exposure of the fusion sequences and, hence, is needed for cell entry. The nature of the cell protease that cleaves the S glycoprotein varies according to the coronavirus. The MERS-CoV S glycoprotein contains a furin cleavage site and is probably processed by these intracellular proteases during exit from the cell. The virus particles are therefore ready for entry into the next cell. In contrast, the SARS-CoV S glycoprotein is uncleaved upon virus release from cells; it is likely cleaved during virus entry into a cell. Furin proteases may, therefore, be an option for therapeutic uses.

Virus replication: Depending on the type of virus, polymerases, replicases, proteins for translocation, and assembling are needed for replication. Coronaviruses all encode 15–16 replicase related proteins, 4–5 structural proteins, and 1–8 group-specific or accessory proteins. Many of the replicase proteins are assembled into replication machinery in double-membrane vesicles (DMVs) and are located on a reticular network of membranes that are derived from the endoplasmic reticulum [28].

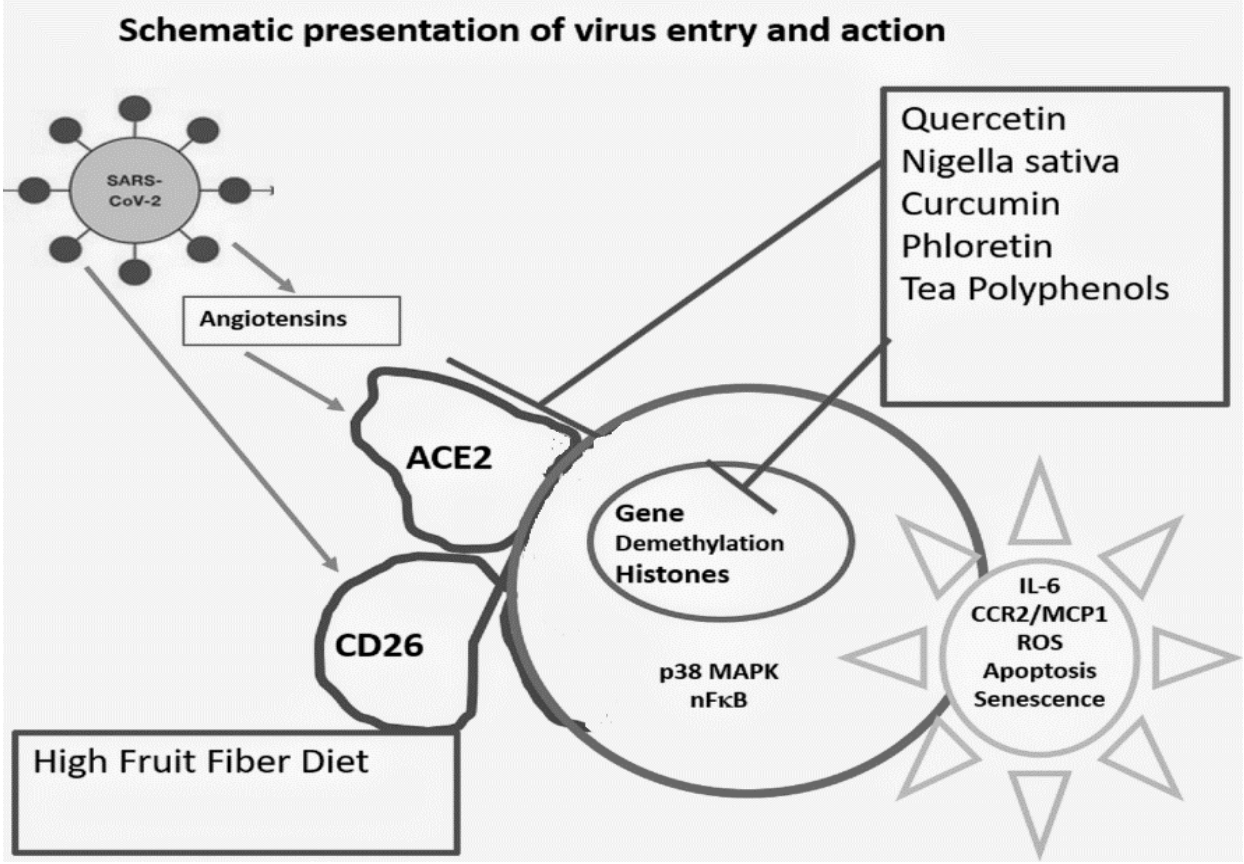

Figure 1. This is a schematic presentation of virus entry via ACE2 (=Angiotensin-converting enzyme 2) and/or CD26 (=Dipeptidylpeptidase 4 also known as DPP4). Consequences for epigenetic regulation of genes involved in inflammation, especially Il-6, apoptosis, and senescence, including prominent intracellular mediators such as p38 MAPK (p38 class of mitogen-activated protein kinase) and transcription factor NF-kB (=nuclear factor 'kappa-light-chain-enhancer).

Immune skewing: Viruses have developed an arsenal of strategies to not only avoid immune detection, but to actively manipulate host immune responses and create an environment more favorable for infection. Viruses have found ways to alter the CD4 T cell response by skewing response away from the Th1 phenotype or inducing regulatory CD4 T cell (Treg) responses to maintain viral persistence. Respiratory syncytial virus (RSV) has been found to influence the

polarization of CD4 T cells into different phenotypes and NS1 inhibits MHC expression. This results in reduced CD4 T cell polarization, inhibition of proliferation for Th17 cells, and the promotion of activation for Th2 cells. HCMV virus was found to induce IL-10 and TGF-β production by CD4 T cells and EBV can down modulate MHC class I expression and viral G protein-coupled receptor. Similarly, BILF1 can inhibit the expression of multiple HLA molecules. The influenza virus directly infects antigen-specific B cells in the lungs resulting in the death of the infected cell and reduced antibody response [29].

The NSP1, ORF6, and N proteins from SARS-CoV, the NS1 protein from influenza virus, the VP35 and VP24 proteins from the Ebola virus (the leader protein from picornaviruses), and the V proteins from Nipah and Hendra viruses have each been identified as immunomodulating proteins. Each protein blocks one or more key signaling proteins in the IFN and NF-κB pathways to enhance viral replication and pathogenesis. The influenza virus NS1 protein affects the IRF3 signaling pathway as well as mRNA stability and trafficking. SARS-CoV and MHV, both group II coronaviruses, have been shown to interact intimately with the innate immune response [30-36]. As reported for other viruses, the coronavirus-host interplay and response outcome are highly dependent on cell type, virus concentration, and whether results are obtained from in vitro or in vivo experimentations. MHV and SARS-CoV induce various degrees of IFN as well, depending on all of these variables; type I IFN expression was found to be induced following SARS-CoV infection. Various degrees of induction have been found in cell lines from very high early levels that diminish during infection, to very high levels only late in infection, to no induction of IFN at all. The reasons behind these differences are currently not well understood. The interaction between SARS-CoV and the innate immune system appears to be tightly balanced during infection. In macrophages and dendritic cells (DCs), SARS-CoV has been shown to induce type I IFN mRNA production. Additionally, SARS-CoV and MHV have been shown to produce large amounts of IFN-inducing dsRNA while not inducing IFN in those cells. Although mechanistically unclear, several possibilities are under investigation. The viruses may be encoding proteins (IFN antagonists) that directly inhibit the signaling pathways that are responsible for IFN induction. Significant amounts of data support the hypothesis that coronaviruses encode one or more IFN antagonist genes [37].

Aging and viral infection: Interactions between aging and viral infection may partially explain the higher susceptibility of older citizens to viral infections, as reported for SARS-CoV-2. A functional association between COVID-19 infection and the process of chronological aging is under discussion [21]. The two host receptors proposed for COVID-19, ACE-2, and CD26, both show associations with senescence. Similarly, two proposed therapeutics for the treatment of COVID-19 infection are Azithromycin and Quercetin, both drugs with significant senolytic activity. Also, Chloroquine-related compounds inhibit the induction of the well-known senescence marker, beta-galactosidase [27].

Several developments in the course of human aging favor viral infection. Alterations in the immune system are a crucial component of aging that can manifest as a decreased ability to fight infection, a diminished response to vaccination, increased incidence of cancer, higher prevalence of autoimmunity, and low-grade inflammation, among others. In the human hematopoietic system, aging is associated with a decrease in the cellularity of the bone marrow, a decline in the adaptive immune response, and an increase in hematological disorders. The changes observed in hematopoietic stem cells with age play an important part in the generation of the T and B cell repertoire. In the case of T cells, this is compounded by thymic involution and the decline in its function. Similarly, B cells undergo age-related changes in their repertoire. Cellular senescence is a state of permanent cell cycle arrest associated with a stereotyped set of phenotypic alterations [38]. Senescent T cells have a high secretory capacity, which may be a modified version of the senescence-associated secretory phenotype (SASP) [39]. The

immunosenescence is characterized by a particular "remodeling" of the immune system, induced by oxidative stress. Apoptosis also plays a central role in old age, a period in which the ability of apoptosis can change. The remodeling of apoptosis together with the inflammaging and the up regulation of the immune response with the consequent secretion of pro-inflammatory lymphokines represents the major determinant of the rate of aging and longevity. Inflammaging is a hallmark of aging and the chronic stimulation of the immune system by viruses such as cytomegalovirus (CMV) elicits the production of proinflammatory cytokines by cells of both the innate and adaptive immune system. The decline in the adaptive immune system with age also decreases its ability to effectively contain viral infections, thereby extending the duration of innate immune response and its consequences [40, 41].

Viral infections were seen to accelerate human aging, as seen on their effects on the CpG methylation of the epigenetic clock. Infections also trigger a DNA damage response. Additionally, DNA instability and an impaired DNA repair system are speculated to favor viral infections [42-44].

Biological opportunities for intervention with viral infections, epigenetics: Research identifying SARS-CoV-2-human protein-protein interactions indicated interactions between SARS-CoV-2 proteins and epigenetic regulators of gene expression such as histone deacetylase 2 (HDAC2) [45]. Epigenetic reprogramming is discussed as a major possibility to control viral gene expression or latency. Reactivating HCMV from the latent phase or repressing the viral lytic and reactivation phases by epigenetic-targeted therapy are also options to overcome latency, viral shedding, replication, and infectivity. This could eventually lead to the control of infection and its complications. This concept is similarly studied in the context of hepatitis B and C viruses, herpes simplex virus, and Epstein-Barr virus. SIRT3, a class III HDAC, restricted HBV cccDNA transcription. Treatment with the small molecule C646 that specifically inhibits p300/CBP, the histone acetyltransferases (HAT) for H3K27ac, and H3K122ac was shown to reduce HBV transcription in a dose-dependent manner [46, 47]. Like other ssRNA viruses, when SARS-Cov-2 infects host cells, the virus requires continuous cellular transcription for viral mRNA synthesis. This mechanism implies a functional association with the host's genome expression so that it adapts the infected cell for the host-to-pathogen confrontation at each replication. RNA viruses can also recruit host DNA methyltransferases (DNMTs) to methylate and decrease gene expression of specific genes including those for shaping innate and adaptive immune responses [48-50]. Inhibition of DNMTs will re-activate the immunity-related gene function responsible for combating viral infection. RNA methyltransferases include enzymes such as METTL3/14 that may facilitate RdRP stability and protect the mRNA cap guanine-N7-methyltransferase that is responsible for protecting the virus's ability to replicate [51, 52]. This is because RNA methyltransferases include enzymes such as METTL3/14 that may facilitate RdRP stability and protect the mRNA cap. Coronavirus nsp10/nsp16 methyltransferase can be targeted to reduce replication and pathogenesis [133].

RESULTS

Role of bioactive plant ingredients: At the time of the Severe Acute Respiratory Syndrome, SARS, outbreak from 2002-2003, the WHO initiated an International Expert Meeting to review and analyze clinical reports on combination treatments for SARS. The report of the WHO International Expert Meeting reviews and analyzes clinical reports on combination treatments for SARS which combine Traditional Chinese medicine and Western medicine. It summarized not only mechanisms of infections and case studies, but also various combinations of therapy. Nutraceuticals and functional foods have broad potential for preventing the mechanisms of viral infection and modulating immune responses.

Table 1: Overview of the plant extracts, plant sources, recommended daily intake range, concentrations in foods, target virus, and mode of interaction.

Compound	Source	Recommended Daily Intake Range	Food Concentration/ 100g	Target Virus	Effectiveness Against Virus	Literature
Quercetin	E.g. Onions, capers, chives	50-800 mg	Up to 234 mg	Influenza A Virus (H5N1), SARS	Interaction with the HA2 subunit to inhibit the entry of the H5N1 virus inhibitory activity in the early stage of influenza infection inhibits docking station Angiotensin-Converting Enzyme	53-59
Curcumin	Turmeric	3 mg/kg body weight	3000 mg	Influenza virus, hepatitis C virus, Zika virus (ZIKV), human immunodeficiency virus (HIV), herpes simplex virus 2 (HSV-2), human papillomavirus (HPV), chikungunya virus (CHIKV)	Binding to three protein receptors: RBD-S (PDB ID:6LXT), PD-ACE2 (PDB ID:6VW1), and SARS-CoV-2 protease (PDB ID:6LU7)	63-66
Epigallocatechin gallate (EGCG)	Green tea	130 mg	7380 mg	Herpes simplex virus, adenovirus, human papillomavirus, hepatitis B and C virus, Zika virus (ZIKV), dengue virus, chikungunya virus (CHIKV), human immunodeficiency virus (HIV), West Nile viruses	Senescence increases viral and cellular membrane permeability; interactions of EGCG with DNMTs, ACE-2, and helicase. Inhibits SssI DNMT- and DMTI-mediated DNA methylation	69-108
Phloretin	E.g. Apples, pears, or strawberries	40 mg	0.65 mg	ZIKV (MR766 and PRVABC59)	Influences the charge, fluidity, and permeability of the cells; it regulates interleukin 6, interleukin 8, and TNF alpha via epigenetic mechanisms and deprives the viruses of the nutrients, reduced reproducibility	11-113
Berberine	Barberry, turmeric	<1500 mg	1.6-4.3 mg	Influenza (H1N1), chikungunya virus (CHIKV)	Reduction in viral titers and course of the disease; reduction of all major virus-induced MAPK pathways. Suppression of tumor necrosis factor (TNF)-α-induced nuclear factor (NF)-κB activation	11-116

Compound	Source	Recommended Daily Intake Range	Food Concentration / 100g	Target Virus	Effectiveness Against Virus	Literature
Sulforaphane	Broccoli	400 mg	1400 mg	Live attenuated influenza virus (LAIV)-eppstein bar Virus (EBV)	Induces peripheral blood NK cell activation; SFN induces active DNA demethylation via the up regulation of the Tet genes *in vitro*. Chromatin reprogramming	119
Thymoquinone	Nigella sativa, black seed oil	Up to 500 mg		Avian influenza virus (H9N2)	Reduced the virus pathogenicity, DNA methylation/demethylation [upregulation of ubiquitin-like-containing plant homeodomain (PHD)]	127
Polyphenols from Sage (E.g. salvin)	Sage, *Salvia officinalis*	150 mg	450 mg	HSV 1-herpes simplex virus, human immunodeficiency virus (HIV), SARS-CoV	Efficacy in anti-HSV before absorption stage; no efficacy in the replication stage	12, 131

Quercetin: Quercetin, a flavonoid found in fruits and vegetables, has unique biological properties that may improve mental or physical performance and reduce infection risk. These properties include many potential benefits to overall health and disease resistance including anti-carcinogenic, anti-inflammatory, antiviral, antioxidant, and psychostimulant activities. Additionally, it facilitates the ability to inhibit lipid peroxidation, platelet aggregation, capillary permeability, and the stimulation of mitochondrial biogenesis. Flavonoid molecules are widely distributed in plants. They are found in a variety of foods including apples, berries, Brassica vegetables, capers, grapes, onions, shallots, tea, and tomatoes, as well as many seeds, nuts, flowers, barks, and leaves. Quercetin is also found in medicinal botanicals, including *Ginkgo biloba*, *Hypericum perforatum*, and *Sambucus canadensis.* The recommended intake of quercetin was reported to be 4.37 mg/day and the main food source for flavonol is apples (7.4%). However, capers have the highest concentration containing 234 mg of flavonol per 100 g of edible portions.

The dietary intake of quercetin ranges from 50 to 800 mg/day. Evidence indicates that quercetin glucosides are far better absorbed than rutinosides (the major quercetin glycoside in tea). Quercetin and its derivatives are transformed into various metabolites (phenolic acid) by enteric bacteria and enzymes in intestinal mucosal epithelial cells. Quercetin was reported as a long-lasting anti-inflammatory substance that possesses strong anti-inflammatory capacities. Several studies *in vitro* using different cell lines have shown that quercetin inhibits tumor necrosis factor (TNF-) and IL-8 production in cells. Protective effects of quercetin against inflammation in human umbilical vein endothelial cells (HUVECs) indicated that the effect was mediated via the downregulation of vascular cell adhesion molecule 1 (VCAM-1) and CD80 expression. Quercetin was also found to decrease stress-induced senescent cells and to suppress the senescence-associated pro-inflammatory response [39]. Quercetin significantly induces the gene expression and production of Th-1 and derived interferon- (IFN-) and down-regulates Th-2 derived interleukin 4 (IL-4) by normal peripheral blood mononuclear cells. Quercetin inhibited influenza infection with a wide spectrum of strains with its half-maximal inhibitory concentration (IC50) between 7.756 and 1.931 g/mL. Mechanism studies identified that quercetin also interacts with the HA2 subunit [134]. The viral HA2 subunit is known as a target for antiviral vaccines. Thus, an interaction with HA2 by quercetin could have an antiviral effect. Moreover, quercetin could inhibit the entry of the H5N1 virus. This study indicates that the inhibitory activity of quercetin in the early stage of influenza

infection provides a future therapeutic option to develop effective, safe, and affordable natural products for the treatment and prophylaxis of IAV infections [53-59]. Quercetin, like some other flavonoids, inhibits Angiotensin-Converting Enzyme, a known docking station of SARS. IC_{50}values for luteolin, quercetin, rutin, kaempferol, rhoifolin, and apigenin K were 23, 43, 64, 178, 183, and 196 µM, respectively [60, 61].

Curcumin: The polyphenol curcumin aids in the management of oxidative and inflammatory conditions, metabolic syndrome, arthritis, anxiety, and hyperlipidemia. Ingesting curcumin by itself does not lead to the associated health benefits due to its poor bioavailability, which appears to be primarily due to poor absorption, rapid metabolism, and rapid elimination. Several components can increase bioavailability. For example, piperine is the major active component of black pepper and, when combined in a complex with curcumin, has been shown to increase bioavailability by 2000% [135]. Curcumin combined with enhancing agents provides multiple health benefits. Curcumin can reduce different forms of free radicals, such as reactive oxygen and nitrogen species and modulate the activity of GSH, catalase, and SOD enzymes active in the neutralization of free radicals. Additionally, it can inhibit ROS-generating enzymes such as lipoxygenase/cyclooxygenase and xanthine hydrogenase/oxidase. Curcumin has been shown to block NF-B activation increased by several different inflammatory stimuli such as markers of inflammation (soluble CD40 ligand, sCD40L), interleukin 1 beta (IL-1), interleukin 6 (IL-6), and soluble vascular cell adhesion molecule 1 (sVCAM-1).

Curcumin shows antiviral and antibacterial activity against the influenza virus, hepatitis C, HIV, and strains of *Staphylococcus*, *Streptococcus*, and *Pseudomonas*. Antiviral activity was observed against several different viruses including hepatitis viruses, influenza viruses, and emerging arboviruses like the Zika virus (ZIKV) and chikungunya virus (CHIKV). Interestingly, it has also been reported that the molecule inhibits human immunodeficiency virus (HIV), herpes simplex virus 2 (HSV-2), and human papillomavirus (HPV). Furthermore, a modest inhibition of the HIV-1 and HIV-2 proteases was shown following its use [62]–[66]. Compounds contained in Curcuma sp.*,* Citrus sp.*, Alpinia galanga,* and *Caesalpinia sappan* were evaluated as anti-SARS-CoV-2 inhibitors through their binding to 3 protein receptors. The selected protein receptors were RBD-S (PDB ID:6LXT), PD-ACE2 (PDB ID: 6VW1), and SARS-CoV-2 protease (PDB ID:6LU7). The affinities of the bonds formed were represented as a docking score. The results showed that hesperidin, one of the compounds in Citrus sp., has the lowest docking score for all three protein receptors, representing the highest affinity for binding to the receptors. Moreover, all of the citrus flavonoids as well as curcumin, brazilin, and galangin possess a good affinity to the receptors, indicating that those compounds may have inhibitory functions for the viral infection and replication. In general, docking studies indicate that *Citrus sp*. exhibits the best potential as an inhibitor to the development of the SARS-CoV-2, followed by galangal, sappan wood, and *Curcuma sp*. [67].

Epigallocatechin gallate (EGCG): Green tea EGCG was shown to provide a plethora of beneficial effects for human health in areas relating to inflammation, metabolic disease, premature aging, and neurological diseases. These compounds primarily exhibited antioxidative and anti-inflammatory activities as well as the modulation of epigenetic methylation, histone modification, and miRNAs, and the facilitation of DNA stability and repair. [68-74]. Additionally, senescence, an import mechanism for viral infection, is addressed by EGCG [75-77]. EGCG has been reported to possess a broad spectrum of antiviral activities against DNA viruses such as herpes simplex virus (HSV; Herpesviridae), adenovirus (Adenoviridae), human papillomavirus (HPV; Papovaviridae), and hepatitis B virus (HBV; Hepadnaviridae). It was also shown to help prevent (+)-RNA viruses such as hepatitis C virus (HCV; Flaviviridae), Zika virus(ZIKV; Flaviviridae), dengue virus (DENV; Flaviviridae), West Nile viruses (WNV; Flaviviridae), and Chikungunya virus (CHIKV; Togaviridae) as well as (−)-RNA viruses such as human immunodeficiency virus (HIV; Retroviridae), Ebola virus (EBOV; Filoviridae) and influenza virus (Orthomyxoviridae) [78, 79, 88-97, 80, 98-106, 81-87].

EGCG-fatty acid derivatives are expected to increase viral and cellular membrane permeability. EGCG-fatty acid monoesters showed improved antiviral activities against different types of viruses, most likely due to their increased affinity for viruses and cellular membranes [106].

Antiviral mechanisms may come from the interactions of EGCG with DNMTs, ACE-2, and helicase [51]. Tea polyphenols [catechin, epicatechin, and (-)-epigallocatechin-3-O-gallate (EGCG)] and bioflavonoids (quercetin, fisetin, and myricetin) inhibited SssI DNMT- and DNMT1-mediated DNA methylation in a concentration-dependent manner [39]. The IC(50) values for catechin, epicatechin, and various flavonoids ranged from 1.0 to 8.4 microM, but EGCG was a more potent inhibitor, with IC(50) values ranging from 0.21 to 0.47 microM [107, 108].

Phloretin: Phloretin is one of the best known and most abundant dihydrochalcones characterized by the presence of the 2,6-dihydroxyacetophenone pharmacophore. It is a versatile molecule with anticancer, anti-osteoclastogenic, antifungal, antiviral, anti-inflammatory, antibacterial, and estrogenic activities which also has the ability to increase the fluidity of biological membranes. The fluidity is needed for proteins and biomolecules of the membrane to be able to rotate and diffuse for intracellular communication. The main biological action of phloretin is the inhibition of glucose cotransporter 1. Phloretin also possesses antioxidative properties and affects the synthesis of proinflammatory molecules like PGE2, IL-8, IL-6, MCP-1, and ICAM-1. Phloretin has also been shown to prevent TNF-α-stimulated upregulation of VCAM-1, ICAM-1, and E-selectin expression in a concentration-dependent manner. To the same extent as for TNF-α, phloretin also inhibited IL-1β-induced upregulation in the expression of all 3 adhesion molecules. The inhibition of cytokine-induced adhesion molecule expression for VCAM-1, ICAM-1, and E-selectin has already been detected already at the level of mRNA [109-111]. Phloretin also significantly decreased infectious titers of two ZIKV strains. The 50% effective concentration (EC 50) of phloretin against MR766 and PRVABC59 was 22.85 µM and 9.31 µM, respectively. Further analyses demonstrated that decreased viral production was due to host-targeted inhibition, including decreased apoptotic caspase-3 and -7 activities and reduced phosphorylation of Akt/mTOR pathways. Additionally, upon the disruption of cellular glucose availability within host cells using 2-deoxy- d -glucose, ZIKV propagation was inhibited [109-113].

Berberine: In Chinese medicine, berberine has a strong importance in the clinical therapy of influenza virus infections. Berberine is an isoquinoline derivative alkaloid isolated from many medicinal herbs such as Rhizoma coptidis and Cortex phellodendri [114]. The activity of berberine as an antiviral substance was also shown against a variety of strains of the chikungunya virus (CHIKV). CHIKV infection specifically activated the major mitogen-activated protein kinase (MAPK) signaling pathways including extracellular signal-related kinase (ERK), p38, and c-Jun NH2-terminal kinase (JNK). Upon treatment with berberine, this virus-induced MAPK activation was markedly reduced. Subsequent analyses with specific inhibitors of these kinases indicated that the ERK and JNK signaling cascades are important for the generation of progeny virions. In contrast to specific MAPK inhibitors, berberine lowered virus-induced activation of all major MAPK pathways, resulting in a stronger reduction of viral titers. Furthermore, a significant reduction of CHIKV-induced inflammatory disease was also observed with berberine in a murine models [115].

The MEK-ERK signaling pathway and autophagy also play an important role in the pathophysiology of enterovirus71 (EV7l1) replication. Inhibition of the MEK-ERK signaling pathway and autophagy [116] was shown with the isoquinoline alkaloid isolated from Berberis vulgaris L. [117]

Berberine derivatives were also previously evaluated for their ability to suppress tumor necrosis factor (TNF)-α-induced nuclear factor (NF)-κB activation [118].

Sulforaphane: Originally defined to support bone health [119], the naturally occurring isothiocyanate sulforaphane (SFN) has also been shown to have antiviral activity. It has been previously observed that the osteoblast supporting transcription factor Runx2 is required for the long-term persistence of antiviral

CD8+ memory T cells [120]. Supplementation of an SFN-rich broccoli homogenate further increased live attenuated influenza virus (LAIV)- induced granzyme B production in NK cells and granzyme B levels appeared to be negatively associated with influenza RNA levels in nasal lavage fluid cells. The authors concluded that nasal influenza infection may induce complex changes in peripheral blood NK cell activation and that SFN increases virus-induced peripheral blood NK cell granzyme B production, an effect that may be important for enhanced antiviral defense responses [121]. These results show that SFN induces active DNA demethylation via the up-regulation of the Tet genes in vitro. This epigenetic reprogramming of the chromatin leads to apoptosis of preosteoclasts but only to a lower extent of preosteoblasts. A recent study shows that significantly higher mRNA levels of Notch2, Jagged1, RANKL, and IL-1β were observed in EBV positive compared to EBV negative periodontitis lesions suggesting that RANKL, Notch2, and IL-1β play a role in viral defense [122-125].

Nigella sativa, Thymoquinone: Nigella sativa (N. Sativa) is a widely used medicinal plant throughout the world. N. Sativa has been traditionally used for the treatment of a variety of disorders, diseases, and conditions pertaining to the respiratory system, digestive tract, kidneys, liver, and cardiovascular and immune systems. A recent publication showed that an extract containing Nigella sativa oil supported the immune response and reduced the pathogenicity of the H9N2 avian influenza virus, which is structurally related to SARS-CoV-2 in chicken. Many active compounds have been isolated, identified, and reported so far in different varieties of black seeds. The most important active compounds are thymoquinone (30%-48%), thymohydroquinone, dithymoquinone, p-cymene (7%-15%), carvacrol (6%-12%), 4-terpineol (2%-7%), and t-anethol (1%-4%). The most important compound of N. Sativa is Thymoquinone (TQ) which is known for epigenetic action [126-129, 130].

Thymoquinone is known to influence the epigenetic machinery, like modifying histone acetylation and deacetylation, DNA methylation and demethylation, which are among the major epigenetic changes that target inflammatory mediators in various diseases including cancer. Ring finger domain 1 (UHRF1) influences cancer cells by repressing tumor suppressor genes through their promoter hypermethylation during cell proliferation. Thymoquinone can suppress UHRF1 and, thus, might be able to repair epigenetic aberrations in cancer cells through a DNA demethylating process, most likely through the downregulation of DNA methyltransferase 1 (DNMT 1).

Salvia officinalis: In addition to antibacterial action, S. officinalis has been reported to induce antifungal, antiviral, and antimalarial effects. The antiviral activity of S. officinalis is most probably mediated by safficinolide and two antiviral diterpenoids, safficinolide and sageone, can be isolated from the aerial parts of Salvia officinalis. [126, 131].

CONCLUSIONS

The discussed interactions between the mechanism of bioactive plant ingredients and viral mechanisms, especially SARS-related infections, give some hope of plant-derived regiments facilitating pre-interventions or combinations with pharmaceutically derived medication. A better understanding of the interactions of molecules involved in the epigenetic regulation of viral infection and senescence should also booster the development of functional foods for immune-senescence and healthy aging [10, 70, 132].

List of Abbreviations: BILF1, G-protein coupled receptor BILF1, Epstein-Barr virus; cccDNA, covalently closed circular DNA; dsRNA, Double-strand RNA; DNMT1 DNA (cytosine-5)-methyltransferase 1; EBV, Epstein-Barr Virus; H3K27ac epigenetic modification to the DNA packaging protein Histone H3; H3K122ac, Acetylation of histone H3K122; HCMV, Human Cytomegalovirus; HDAC, Histone deacetylase; HLA, Humane Leukozyten Antigen-System; ICAM-1, Intercellular Adhesion Molecule 1, also known as CD54; IAV, Influenza A Virus; IRF3, Interferon regulatory factor 3; IFN, Interferon; IL-10, Interleukin 10; MAPK, Mitogen-activated protein kinases; MCP-1, Monocyte chemoattractant protein-1 (MCP-1/CCL2); MHC, Major Histocompatibility Complex; NF-κB, nuclear factor 'kappa-light-chain-enhancer; NK cell, Natural killer cell; NS1 Nonstructural protein 1,

Dengue; p300/CBP, p300-CBP coactivator family, CREB binding protein; PGE2, Prostaglandin E2; R SssI DNMT, CpG DNA methyltransferase from Spiroplasma sp., strain MQ-1; M.SssI; dRP, RNA-dependent RNA polymerase; SIRT3, NAD-dependent deacetylase sirtuin-3; TGF-β, transforming growth factor-beta; VCAM-1, Vascular cell adhesion protein 1 or cluster of differentiation 106 (CD106).

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