Review Article

Antiviral and Anti-SARS-CoV-2 Activity of Natural Chlorogenic Acid and Its Synthetic Derivatives

Buthaina Mohammed Aljehany[1*]

[1]Department of Food and Nutrition, Faculty of Human Sciences and Design, King Abdulaziz University, Jeddah, Saudi Arabia.

Abstract

Since the dawn of time, several viral epidemics have swept the globe, among them the current COVID-19 outbreak. The ongoing emergence and propagation of novel viral illnesses have compelled researchers to seek new therapeutic approaches that can get beyond the drawbacks of antivirals that are available right now. Medicinal plants have historically offered treatments for a range of illnesses. These bioactive compounds serve as the foundation for many "modern" pharmaceuticals. One of the essential polyphenols in various medicinal plants is Chlorogenic acid (CA), an ester of caffeic and quinic acid. Extensive research has revealed that CA possesses anti-inflammatory, anticarcinogenic, and antioxidant properties. This review aims to briefly summarise CA and its derivative's antiviral properties on various human viral diseases and their ability to fight the current COVID-19 disease. This review summarises CA antiviral action on the following viruses: influenza A virus (H1N1/H3N2/H7N9), hepatitis C virus (HCV) and hepatitis B virus (HBV), human immunodeficiency virus (HIV), infectious bronchitis virus (IBV), porcine reproductive and respiratory syndrome virus (PRRSV), herpes simplex virus (HSV)-1, enterovirus 71 (Ent 71), adenoviruses (AdenV), and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This review will open the way for developing and designing potentially effective and broad-spectrum CA-based antiviral medicines.

Keywords: Chlorogenic acid, Influenza A virus, Hepatitis virus, HIV, SARS-CoV-2

Introduction

As one of the most prevalent beverages worldwide, coffee contains several compounds of the highest health benefits. There are many polyphenols in coffee. One of the most significant coffee polyphenols is 5-O-caffeoylquinic acid, also known as chlorogenic acid (CA). It is an ester of caffeic and quinic acids [1]. Green coffee contains CA, which is also commonly present in many different seeds and fruits, such as blueberries and sunflower seeds. However, ingestion from these sources only makes up around 5–10% of the consumption of coffee beverages. Low quantities of CA are also present in potatoes, tomatoes, apples, pears, and eggplants [2]. Depending on the type of coffee, one cup (200 ml) contains 70-350 mg of CA [3]. According to some research, green Coffea Arabica beans have the lowest average CA content, while green Coffea Robusta beans have the highest average CA content [4, 5]. CA is also found in a variety of plants, including *Lonicera japonica* Thunb, *Eucalyptus globules*, *Crataegus monogyna*, *Vaccinium angustifolium, and Eupatorium perfoliatum* [6]. Besides, it is present in some traditional Chinese medicine (TCM) [7-9].

A growing body of research has shown that CA has anti-inflammatory, anticarcinogenic, and antioxidant characteristics; many epidemiologic studies have focused on these health benefits [10, 11]. It has been demonstrated to be helpful for obesity, type II diabetes, stroke, Alzheimer's disease, endothelial function, and blood pressure [6, 12-15]. CA reduces inflammation produced by viral infections and has antiviral actions against some viruses, such as HIV [16, 17], adenovirus [18], hepatitis B virus (HBV) [18], and HSVs [19, 20]. *In vivo*, CA was revealed to decrease the level of serum HBV [20]. According to the findings of molecular docking tests, CA may be a promising neuraminidase blocker for influenza viruses H1N1 [21], H5N1 [22], and H7N9 [23]. In H1N1-infected mice, CA has restored cell viability and boosted survival rates [21]. The antiviral properties of CA towards influenza virus H5N1[17, 24] and its derivatives towards influenza virus H3N2 [25, 26] have been established in earlier research.

Throughout history, medicinal plants have provided cures for various illnesses. This has prompted numerous studies to

Address for correspondence: Buthaina Mohammed Aljehany, Department of Food and Nutrition, Faculty of Human Sciences and Design, King Abdulaziz University, Jeddah, Saudi Arabia.
baljehany@kau.edu.sa

How to cite this article: Aljehany BM. Antiviral and Anti-SARS-CoV-2 Activity of Natural Chlorogenic Acid and Its Synthetic Derivatives. Arch Pharm Pract. 2022;13(4):74-81. https://doi.org/10.51847/pg8LAD1TQf

pinpoint the metabolites behind these cures. Many "contemporary" pharmacological medications have their roots in these bioactive substances [27, 28]. The general populace is now using natural herbal supplements due to the rise in infectious diseases. One of these compounds, CA, has received attention from the biological and medical communities, and as such, it will likely be covered in upcoming research on medical trends and pharmacology [29]. This review paper aims to give an overview of the *in vivo* and *in vitro* research on CA's antiviral properties, including the anti-SARS-COV2 impacts.

Antiviral Effect of Ca against Influenza a Virus (H1n1/H3n2/H7n9)

Neuraminidase, one of the two glycoproteins present on the surface of the influenza virus, cleaves the neuraminic acid unit and helps spread the breed virus to other airway cells [30]. The most widely prescribed antiviral medications for the treatment of influenza are neuraminidase inhibitors. For this reason, the WHO has exclusively advised neuraminidase inhibitors since 2010 for managing and prophylaxis influenza A and B viruses [31]. The most efficacious neuraminidase inhibitors presently available are zanamivir (Relenza) and oseltamivir (Tamiflu), which are approved for both therapeutic and preventative use globally [32]. CA, which defines all quinic acid hydroxycinnamic acid esters, is surprisingly similar in structure to over-the-counter antiviral drugs such as ostermavir, which have been identified as targeting viral neuraminidase [17, 32]. Using fluorometric experiments, dietary CA showed potent inhibitory effects on neuraminidase from *Clostridium perfringens*, H5N1, and recombinant H5N1 (N-His) tags. The catechol group in CA appears to have had a significant role in the neuraminidase inhibition activity. Hence, CA is categorized as a natural remedy with promising antivirus activity. Therefore, CA is on the list of herbal remedies with promising antiviral effects [17].

The interaction model between CA and the neuraminidase enzyme was basically derived using the molecular docking computation approach. Next, molecular dynamics simulations were conducted to optimize a global 3-D model. The binding free energy between CA and neuraminidase can also be calculated using molecular dynamics data sets. Analyses have also been done on the crucial amino acids in the CA-neuraminidase interaction. The mechanism of CA's suppression of the influenza virus was discussed in terms of structure, energy, and virtual amino acid modification. The findings showed that CA interacted with hydrogen by Arg292, Arg371, Arg118, Glu119, and Glu276 in the surface-active region of neuraminidase, identical to the majority of anti-HIV neuraminidase inhibitors. Additionally, CA did not link with the other amino acids of the NA-150-cavity but instead created a weak interaction in the form of hydrogen bonds with Arg152 of the NA150-cavity [33].

The use of CA in the management of influenza virus infection is possible. In both cellular and animal models, CA inhibits the influenza A virus by acting as a neuraminidase blocker. An investigation of the antiviral properties and probable mechanisms of CA in the treatment of influenza A virus showed inhibitory effects on oseltamivir-resistant strains. The time-lapse analysis demonstrated that CA inhibited the influenza virus later in the infection cycle. Indirect immunofluorescence has demonstrated that CA reduced nucleoprotein (NP) expression. The fact that CA prevented the release of newly generated viral particles from infected cells was supported by the suppression of neuraminidase action. Furthermore, in mice, intravenous administration of 100 mg/kg/d CA exhibited an efficient antiviral effect, imparting 60% and 50% protection from death from H1N1 and H3N2, lowering virus titers, and successfully minimizing airway inflammation [34].

Although the hydrophilic extract of coffee exhibit no restrained action at even doses above 100 g/ml, the hydrophobic portion directly hindered the infection of both the neuraminidase-resistant influenza A/Yokohama/77/2008(H1N1) virus and a seasonal influenza A/Puerto Rico/8/24(H1N1) virus in a concentration-dependent fashion. According to the HPLC analysis, caffeine was found to be the main constituent of the hydrophobic portion. In fact, caffeine by itself exhibited similar anti-influenza viral efficacy. Contrary to CA, which at concentrations lower than 2 mg/ml had no discernible antiviral activity, caffeic acid also prevented viral infection. The direct antiviral action of caffeine's dioctanoyl ester was about 38 times that of caffeine [35].

Four possible blockers for the H7N9 neuraminidase were discovered through molecular docking; these compounds may be helpful for drug-resistant mutations. Baicalein, CA, oleanolic acid, and quercetin all have strong fiting to neuraminidase that are similar to those of oseltamivir. Further research revealed that the R294K mutation in neuraminidase might significantly lower the binding affinity for oseltamivir while maintaining stable interaction with other natural compounds [23].

The anti-H1N1 action of the Brazilian green propolis (BGP) water extract and its components was investigated using cell viability and real-time PCR assays. The results demonstrated that BGP has an anti-H1N1 impact and that CA is the active anti-H1N1 constituent of BGP. Moreover, even in the existence of BGP, the quantity of viral RNA per cell held steady, implying that BGP seems to have no significant impact on the H1N1 virus but could have a cytoprotective function by impacting intracellular functions. CA appear to be the effective anti-H1N1 ingredient of BGP. These findings could help use natural remedies for prophylaxis and develop new anti-influenza medicine dependent on CA [36].

Antiviral Effect of Ca against HCV and HBV

The Hepatitis C virus is a member of the Flaviviridae family. It is an enveloped, positive-sense, single-stranded RNA virus belonging to the genus Hepacivirus [37]. Chronic HCV

disease has been identified as a significant worldwide public health hazard because it is a chief cause of chronic hepatitis, cirrhosis, and liver cancer [38, 39]. Although newer HCV direct-acting antiviral drugs have significantly improved therapeutic efficacy, issues remain [40, 41]. High costs significantly limit most individuals' access to these powerful treatments. Several molecules popular in coffee, such as the hydrophilic group (CA, quinic acid, p-coumaric acid, and tannic acid) and the lipophilic group (kahweol palmitate, methyl 2,5-dihydroxy-cinnamate, cafestol eicosanate, cafestol, cafestol, and cafestol strearate), were investigated for their impact on HCV infection. CA, p-cumaric acid, caffeic acid, and tannic acid were among the hydrophilic substances that appeared to have anti-HCV action; however, no drug in the lipophilic category did [42].

The main epidemiological cause of both acute and chronic hepatitis is human HBV, and those who carry the virus are at significant risk of developing cirrhosis and liver cancer. HepG2.2.15 cells and a duck HBV infection model were employed *in vitro* and *in vivo* to assess CA anti-HBV efficacy. CA prevented the replication of the HBV-DNA and the generation of HBsAg in the cell model. In a model of ducklings with infection (DHBV), CA also decreased serum DHBV levels. Additionally, the anti-HBV activity of coffee bean crude extracts with a high CA concentration was investigated. Both the standard and decaffeinated coffee extracts had inhibitory activity on HBV replication. The decrease of HBV-DNA greater than viral antigens is one of the mechanisms of action for CA against HBV [20].

Antiviral Effect of Ca against Infectious Bronchitis Virus (IBV)

The IBV is a prototype coronavirus among the coronaviruses [43, 44]. This major respiratory pathogen seriously impacts the chicken business [45, 46]. This virus is a member of the genus Gammacoronavirus (Gamma-CoV) and the family Coronaviridae [47]. IBV is an enveloped positive-sense signal-stranded RNA virus that replicates the digestive, respiratory, urinary, and reproductive systems to induce pathological alterations [48-51]. A study focused on the antiviral effect of CA on IBV *in vivo* and *in vitro* found that CA drastically decreased the relative mRNA expression of IBV-N in CEK cells (*in vitro*). CA supplementation at high concentrations (400 mg/kg) decreased IBV mRNA expression levels and improved tracheal and lung damage (*in vivo*). The mRNA expression profiles of NF-κB, IL-6, IL-1, IL-12, and IL-10 were all significantly reduced in the trachea, but IL-22 and IL-10 were increased. Expression of MDA5, MAVS, TLR7, MyD88, IRF7, IFN-α, and IFN-β was significantly increased by high doses of CA in both the trachea and lungs. In addition, high doses of CA significantly promoted CD3+, CD4+, and CD4+ / CD8 + cell proliferation and significantly increased serum of IgG, IgA, and IgM levels. According to these findings, CA is a potent anti-IBV agent that, at high concentrations, strongly regulates innate immunity via the TLR7, NF-κB, and MDA5 signaling pathways, potentially triggering both a humoral and cell-mediated immune response in IBV-infected chickens [52].

Antiviral Effect of Ca against Human Immunodeficiency Virus (HIV)

Some CA secondary metabolites have significant roles in enhancing immune function and have the promise to be antiviral, including HIV [53]. Currently available anti-HIV reverse transcriptase and anti-HIV protease medications are used to treat HIV infection [54]. Numerous HIV reverse transcriptase and protease inhibitors have been identified in plant and marine species [55-59].

Metabolomic studies of plants are crucial for connecting biological action to the chemical makeup of extracts [60]. In a recent study, metabolomics was employed to detect anti-HIV chemicals isolated from 57 Helichrysum species. The results of the NMR-based metabolomic study revealed that the main anti-HIV chemicals in the Helichrysum species were quinic acid, compounds with cinnamoyl functional groups, and compounds with CA. This study also demonstrated that quinic acid and CA-type chemicals are indicators of anti-HIV efficacy [61].

Morus alba L., family Moraceae, 1 mg/mL dose increased cell viability (57.94%) and HIV suppression rate (74.95%) relative to zidovudine's 87.87% and 79.81%, respectively. One of the active components in *Morus alba* L. was discovered to be neochlorogenic acid. Neochlorogenic acid significantly reduced the total reverse transcriptase gene expression identified by PCR compared to the control (6.01 versus 35.42, p 0.0001). Neochlorogenic acid may have an effect on sarcoma, the epidermal growth factor receptor, and hemopoietic cell kinase, thus suppressing HIV-1 infection, according to an enrichment study [62].

HIV+/AIDS patients have a significant chance of complications due to the HIV antiretroviral medication like resistance and becoming orally colonized by Candida albicans and non-albicans Candida variants that are refractory to antifungals. In the following examination, a methanolic (MeOH) extract from Heteropterys brachiata is assessed for its potential anti-HIV and anti-Candida properties. The reverse transcriptase of the HIV-1 enzyme was used as an enzymatic target to evaluate the anti-HIV impact. The anti-candidal action was also assessed by employing the Candida albicans strain ATCC® 90028 and according to a defined test technique for yeast. Heteropterys brachiata MeOH at 1 mg/mL concentration inhibits RT-HIV by 38.5 percent, whereas at 10 mg/mL concentration, it inhibits Candida albicans development by 98 percent. These results indicate that the MeOH extract of Heteropterys brachiata has a high anti-candidal impact and a weak anti-HIV effect [63].

Another research examined the anti-HIV-1 reverse transcriptase activity of 3 flavones, genkwanin, hispidulin, and cirsimaritin, as well as 8 CA derivatives, including 3,4-di-O- caffeoylquinic acid, 4,5-di-O-caffeoylquinic acid, 3,5-

di-O-caffeoylquinic acid methyl ester, 3,5-di-O-caffeoylquinic acid, 3,4,5-tri-O-caffeoylquinic acid methyl ester, 3-O-caffeoylquinic acid, 4-O-caffeoylquinic acid, and 5-O-caffeoylquinic. They were all separated from *Moquiniastrum floribundum* family Asteraceae. The most effective substance was 4,5-di-O-caffeoylquinic acid, with an IC50 of 0.240 mmol/L and 65.0 ± 7.9 percent inhibition on HIV-1 reverse transcriptase [64].

Helichrysum species are considered a valuable source for developing novel anti-HIV chemical compounds. Five helichrysum species had considerable anti-HIV efficacy, with concentrations 12 to 21 g/mL (IC50). 3-dicaffeoylquinic acid compounds, including 3,4-dicaffeoylquinic acid, 3,5-dicaffeoylquinic acid, and 4,5-dicaffeoylquinic acid, along with 2-tricaffeoylquinic acid compounds, including 1,3,5-tricaffeoylquinic acid and either 5-malonyl-1,3,4-tricaffeoylquinic or 3-malonyl-1,4,5-tricaffeoylquinic acid, were found to be the anti-HIV components [55].

HIV integrase, a crucial enzyme that facilitates the integration of the HIV genome into the host chromosome, is an underresearched treatment option [65]. Molecular docking studies investigated how CA inhibits HIV-I integrase and protease. Naturally occurring CA is an excellent integrase blocker but an ineffective protease blocker. A novel receptor for 3,4-O-dicaffeoylquinic acid has been discovered between the chains of HIV-I integrase, potentially disrupting the enzyme's catalytic function [66].

Evaluations were made of the anti-HIV-1 integrase properties of 5-dicaffeoyl-muco-quinic acid, caffeoyl quinic acid, (-) 3, (-) 3, 5-dicaffeoyl quinic acid, (-) 5-caffeoyl quinic acid, and (-) 4, 5-dicaffeoyl quinic acid isolated from the aerial portions of *Aster scaber* family Asteraceae. The antiviral activity of (-) 3, 5-dicaffeoyl-muco-quinic acid was strong, with an IC50 value of 7.01.3 g/ml [67].

From the cultivated cells, 3,4,5-tricaffeoylquinic acid was extracted, which is absent from the entire plant of lettuce leaves. The two main compounds produced by the whole plant were chlorogenic acid (3-caffeoylquinic acid, or CA) and chicoric acid (dicaffeoyl tartaric acid, or CHA). The study tested 3,4,5-tricaffeoylquinic acid's ability to block HIV type 1 integrase. HIV and MT-2 cells' anti-HIV activity was 1.15 M, and the IC50 for HIV integrase was 0.063 M. Between CHA and other CA, 3,4,5-tricaffeoylquinic acid had the strongest HIV-inhibitory effects [16].

In vitro tests show that CA and dicaffeoyltartaric acids have strong inhibitory effects on HIV integrase and stop HIV replication in vitro. From 150 to 840 nM, the CA and dicaffeoyltartaric acids suppressed HIV-1 integrase. They prevented the reproduction of HIV at doses ranging from 2 to 12 mM. They were active against reverse transcriptase at concentrations as low as 7 mM and as high as 100 mM. Over 80 mM levels were required to prevent gp120 from interacting with CD4. Both substances didn't inhibit HIV-1 RNase H by 50% at doses higher than 80 mM. In addition, no activity was observed when the impacts of the dicaffeoyltartaric acids on reverse transcription in acutely infected inoculated cultures were assessed. Thus, the CA and dicaffeoyltartaric acids show >10- to >100-fold selectivity for HIV integrase. Their action versus integrase in the biochemical analysis aligns with their detected anti-HIV efficacy *in vitro* [68].

It is well established that the porcine reproductive and respiratory syndrome (PRRS) virus (PRRSV) infection can result in immunodeficiency. CA and scutellarin (SC) showed potential *in vitro* anti-PRRSV activity in an investigation evaluating the antiviral effect of 17 traditional Chinese medicine-derived ingredients. The EC50 scores were 270.8 14.6 g/ml and 28.21 26.0 g/ml, in both. The timing of the addition and virus-killing assays demonstrated that the two chemical constituents` anti-PRRSV activity might be attributable to inhibiting the early stages of virus multiplication and/or directly neutralizing the virus. In both cases, the suppression rates of CA and SC were 90.8 percent and 61.1 percent [69].

Antiviral Effect of Ca against Enterovirus 71 (ENT 71)

Enteroviruses are picornaviruses that include more than 70 serotypes, such as enterovirus (Ent) 68-71, 73-78, and 89-91, coxsackievirus A1-22 and 24, coxsackievirus B1-6, echovirus 1-21 and 24-33, and poliovirus 1, 2, and 3 [70, 71]. Ent 71 is a positive-sense, single-stranded RNA virus [72]. Ent 71 induces aseptic meningitis, encephalomyelitis, and acute flaccid paralysis, all proving fatal [73, 74]. A plaque reduction assay revealed an IC50 of 6.3 g/ml for CA on Ent71 replication. CA (20 g/ml) significantly inhibited Ent 71 proliferation between 0 and 10 hours. CA also prevented the transcription and translation of Ent 71 2A in Ent 71-infected RD cells. CA also prevented the production of IL-6, TNF, IFN, and MCP-1 in Ent71-infected RD cells [75].

Antiviral Effect of Ca against Adenovirus (AdenV)

AdenV are double-stranded DNA viruses that owe allegiance to the nonenveloped virus family. Various serotypes correspond with various tissue tropisms and are responsible for various clinical symptoms and illnesses, such as digestive problems, otitis media, rhinitis, conjunctivitis, and keratitis pharyngitis. Ad1, Ad2, Ad3, Ad5, and Ad6 serotypes are endemic and primarily invade kids; the residual serotypes have an epidemic pattern and can invade many people [76]. CA inhibited the replication of AdenV-3 (EC50 = 76), AdenV-8 (EC50 = 108), and AdenV-11 (EC50 = 13.3) [77].

Antiviral Effect of Ca against Herpes Simplex Virus (HSV)-1

CA intervention suppressed the inflammatory response in an HSV-1-infected microglial cell model by down-regulating TLR2, Myd88, and IL-6 signaling and preventing IL-6 secretion [78].

Antiviral Effect of Ca against SARS-COV-2

SARS-CoV-2 is a type of enveloped RNA virus. The virus morphology is similar to other coronaviruses, particularly SARS-CoV and MERS-CoV. The disease caused by SARS-CoV-2 has been dubbed coronavirus disease 2019 (COVID-19) and is still spreading worldwide [79-81]. COVID-19 sick people have flu-like symptoms, fatigue, dry cough, diarrhea, and pneumonia. Acute respiratory distress syndrome, refractory metabolic acidosis, septicemia, and clotting disorder can all occur in serious forms [82].

As a result of Li *et al*. results, CA-mediated modulation of SIRTS is now a promising method for reducing virus-induced inflammation, which may also be essential for acute and long-term COVID-19 diseases. The long-COVID-19 syndrome is characterized by fibrosis coupled with long-lasting low-grade inflammation brought on by unidentified molecular processes. Multiorgan damage is a clinical symptom of the long-COVID-19 condition. Such intricate immune system devastation rationalizes the necessity of systemically acting anti-inflammatory drugs with low toxicity and few negative impacts, which we may anticipate from naturally produced drugs [83, 84].

During the COVID-19 disease outbreak, abnormality of acute lung injury (ALI) and acute respiratory distress syndrome was demonstrated. Intranasal CA (1 and 5 mg/kg) injected into male Balb/c mice stimulated with lipopolysaccharide and polyinosinic: polycytidylic acid to resemble COVID-19 symptoms increased GSH and SOD contents ($p<0.001$) and normalized immune cell-infiltrated bronchoalveolar lavage fluid. CA treatment reduced levels of the proinflammatory cytokines (IL-6, IL-1, and TNF-) in a concentration-dependent manner ($p<0.001$). Besides that, CA protects respiratory and cardiovascular physiology. CA can limit respiratory damage from COVID-19 [85].

Pimenta dioica (L.) Merr leaf extracted in ethyl acetate contains ferulic acid, rutin, gallic acid, and CA, four pharmacologically active compounds. Interesting anti-SARS-CoV-2 actions were observed for rutin, gallic acid, and CA, with IC50 values of 31, 108, and 360 g/mL, correspondingly. Additionally, ferulic acid and rutin therapies were found to have better anti-inflammatory benefits [86].

Many West African nations have wild populations of aromatic and medicinal herbs like *Xylopia aethiopica* (Annonaceae). Dried fruits have historically been used in decoctions as pain relievers, anti-inflammatory agents, and antibiotics. The abundance of phenolics and essential oil components in fruits has been associated with their therapeutic effects. Both pseudoviruses (SARS-CoV-1 and SARS-CoV-2) were successfully fought by CA in the pseudovirus experiment [87].

Since its launch in 2004, Chinese authorities have approved xuebijing (XUE) injections to manage H1N1, H7N9, dengue fever, MERS, and ebola. XUE contained significant amounts of hydroxysafor yellow A, CA, and salvianolic acid B. According to past studies, XUE can inhibit endotoxin, improve immune purpose and microcirculation, and regulate clotting dysfunction. COVID- 19 difficulty breathing, coagulopathy, and microvascular abnormalities are common in corona patients, particularly those with systemic inflammatory response syndrome or/and multiorgan injury. Using XUE at the right time can efficiently reverse the condition and lower fatalities [81].

Conducting in silico analysis for substances that may interfere with viral protein activity is a useful strategy for designing knowledge-based therapeutics. CA and rutin exhibited a strong binding with several viral particles by analyzing the data set from the "Shennong project," an in silico screening of the DrugBank library versus SARS-CoV-2 genes. CA and rutin may help treat and recover COVID-19 patients with mild cases [88].

CA may inhibit COVID-19. The SARS-CoV-2 receptors ACE2 and its co-expressed proteins are thought to be the main route by which SARS-CoV-2 enters target cells and have been connected to SARS-CoV-2 infection. Network pharmacology was employed to examine the process of CA impact on COVID-19. CA might be the key candidate that could cure COVID-19 by neutralizing the TNF and HIF-1 signaling pathways of a total of 70 possible targets relevant to managing COVID-19 [89].

Antiviral Effect of Synthetic Derivatives of Ca

The CA is a good agent for synthesizing derivatives with enhanced or novel biological properties [90]. Two synthetic CA derivatives, 3,4-O-dicaffeoyl-1,5-γ-quinide and three dimethoxycinnamoyl-γ-quinides were tested for *in vitro* antiviral activity versus a panel of 14 human viruses. 3,4-O-dicaffeoyl-1,5-quinide had an antiviral effect versus herpes simplex, adenovirus, and influenza virus. Intriguingly, when testing the agents against the respiratory syncytial virus, the 3,4-O-dicaffeoyl-1,5-quinide showed a strong antiviral impact. Studies on the addition time have shown that this substance affects the intracellular post-invasion replication stage. 3,4-O-dicaffeoyl-1,5-quinide may be a helpful drug against the respiratory syncytial virus, and additional mechanistic studies were warned [91].

In another study, the CA analogue 3-caffeoylquinic acid amide (CAA) was prepared using caffeic acid and quinic acid as precursors. CAA is much more stable than CA and has been found to have similar effects against HCV. CAA effectively prevented oxidative damage of HepG2 cells caused by tert-butyl hydroperoxide [90].

Alpha-glucosidases (α-Glu) are hydrolytic enzymes required for glucose metabolism and glycoprotein production [92]. Glycosylation of viral envelope glycoproteins is necessary for viral pathogenicity [93]. To form mature glycans, HIV glycoproteins must be cleaved at the terminal alpha-glucose

units by α-Glu. Therefore, α-Glu suppression is a hopeful policy for creating new anti-HIV drugs [94]. CA analogs with anti-HIV potency included acetonides of mono-caffeoyl 5,6-anhydroquinic acids (5,6-CAA) and acetonides of CA. The anti-HIV action of 3,4-dicaffeoyl 5,6-CAA was two times that of an established anti-HIV chemical, 3,5-dicaffeoylquinic acid [94].

Conclusion

The CA is a compound commonly biosynthesized in plants and is essential for the body's defense against viruses. Investigations on CA's antiviral properties versus various viruses included those that cause hepatitis C and B, influenza A (H1N1/H3N2/H7N9), IBV, HIV, Ent 71, AdenV, HSV-1, and SARS-CoV-2. The modulatory properties of CA on many proinflammatory molecules make CA derivatives extremely efficacious and secure broad-spectrum antiviral medicines. Furthermore, no clinical research uses CA as a treatment for viruses. Consequently, more in vivo research is required to determine the feasibility of CA as a possible antiviral medicine for human illnesses.

ACKNOWLEDGMENTS: None
CONFLICT OF INTEREST: None
FINANCIAL SUPPORT: None
ETHICS STATEMENT: None

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