

Review Article**INTERACTION BETWEEN ACE 2 AND SARS-COV2, AND USE OF EGCG AND THEAFLAVIN TO TREAT COVID 19 IN INITIAL PHASES****SYED SAIF IMAM*, SYEDA TUBA IMAM^a, MDWASIFATHAR^b, RISHABH KUMAR^a, MD YUSUF AMMAR^c**^{a,c}Department of Pharmaceutical Sciences HIMT College of Pharmacy, 8, Institutional Area, Knowledge Park-1, Greater Noida (UP), India 201301, ^aDepartment of Obstetrics and Gynaecology JLNMC Mayaganj, Bhagalpur, Bihar, India 812001, ^bDepartment of Pharmaceutical Sciences, LLOYD College of Pharmacy, 11, Knowledge Park-2, Greater Noida (UP), India 201306^{*}Email: saifbehappy@gmail.com*Received: 05 Nov 2021, Revised and Accepted: 10 Jan 2022***ABSTRACT**

Covid Virus particles engage with host cells via the ACE-2 and GRP78 receptors, transferring the genome particle to the host cell and transforming it into a replicating machine. RdRP is a key protein in the replication mechanism of all RNA viruses. 3CLpro is a cleavage enzyme that breaks down polyproteins into non-structural polyproteins. All four elements of the Covid viral particle are required for its propagation and action, and blocking any one of them can shut down the entire system. EGCG and Theaflavins are flavonoids that block virus particles from attaching to the host cell's ACE-2 and GRP78 receptors, preventing the genome from being transferred into the cell. EGCG binds to 3CLpro with a molecular docking value of 11.7, while TF3 has a docking score of 10.574, indicating that it prevents host cell contact. TF binds to RdRP with a binding energy of 9.11 kcal/mol, implying that RdRP activities are interfered with. Furthermore, these flavonoids have anti-inflammatory properties and reduce the action of cytokines, which can cause serious respiratory difficulties. Except these two there are many others flavonoids which possess anti-inflammatory and anti-viral properties. All of these data suggest that flavonoids could be a useful treatment for SARS-CoV19; however, the issue of stability and bioavailability arises because it is unstable at lungs pH.

Keywords: EGCG, Theaflavins, Covid-19, ACE-2 receptors, GRP78 receptors, RdRP

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INTRODUCTION

Currently, the globe is dealing with the SARS-CoV19 pandemic, which has affected 264 million people worldwide, killed over 5.2 million people, and destroyed many lives by closing opportunities [1]. After the covid pandemic, millions of individuals are suffering from Anxiety and Depression and there is only a glimmer of hope that life will return to normal [2]. The major issue now is the mutation of SARS-CoV19, which is complicating scientists' efforts to discover a treatment for the outbreak. Although there is no confirmed cure for SARS-CoV19, vaccinations are currently on the market, and treatment advancements may be a better method to save more lives.

SARS-CoV19's S glycoprotein (spikes) binds with the body's ACE 2 receptor site and transfers the viral genome within the host cell. The interaction between SARS-CoV19's S glycoprotein (spikes) and the body's ACE 2 receptor site is the key to understanding how the virus spreads throughout the body, as well as a clue to solving the therapy conundrum [3]. ACE 2 is an aminopeptidase that converts Ang II to Ang (1-7) and is located in the lungs, kidneys, endothelium, and heart, among other places. ACE 2 is found almost everywhere in the body, which is why it spreads so swiftly.

SARS-CoV19 also interacts with the Glucose-Regulated Protein 78kDa (GRP78) receptor site through its S glycoprotein (spikes). GRP78 is an important chaperone that is thought to reside in the endoplasmic reticulum (ER) and regulates the unfolded protein response in cells that have been exposed to ER stress. SARS-CoV19 spreads more easily as a result of this interaction [4].

The replicating components 3CLpro and RdRP are in charge of Covid viral replication in the body of the host [5, 6].

Dengue, Ebola, PRRSV, Chikungunya, HIV, HCV, Influenza A and B, and HSV are among the viruses for which epigallocatechin gallate (EGCG) and theaflavins exhibit antiviral activity. These components also have activity against Covid's body, either at the binding site or on the replication unit.

Both EGCG and Theaflavin have powerful antiviral properties, making them effective in preventing covid infection and pandemic spread.

SARS-CoV2

Coronaviruses are members of the Coronaviridae virus family, which causes sickness in both animals and humans. In humans, it can cause everything from normal cold to Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS), which can lead to serious illness and even death. Even after recovering from the virus, the body's immunity has been weakened to the point where it is now susceptible to other infections such as tuberculosis, hepatitis, and AIDS. There has also been an increase in rare diseases such as black fungus, with cases of black fungus suddenly increasing by many folds due to a decline in immunity [7].

Covid virus is spherical or pleomorphic, with single-stranded, encased RNA, helical symmetry, and a surface covered in club-shaped spikes or S glycoprotein (about 74 spikes). Coronavirus has a non-segmented RNA genome that is linear and positive in sense. The RNA has a 5' methylated cap structure and a 3' poly Adenylated tail, which allows it to connect to ribosomes in host cells and translate viral proteins *in vitro*. The viral replicase gene is made up of two open reading frames (ORFs) 1a and 1b, which together produce two large polyproteins (pp1a and pp1ab) that are processed by viral proteases into 15–16 by viral proteases [8].

The RNA-dependent RNA polymerase is an example of a non-structural protein that is involved in viral RNA synthesis and capping. Structure and accessory proteins are encoded by ORFs in the 3'-terminal one-third of the genome [9].

Subtypes of coronavirus

The International Commission on Classification of Viruses (ICTV)'s Research Group has evaluated the Covid nomenclature and classification. They are now split into three genera: alpha-coronavirus, beta-coronavirus, and gamma-coronavirus, with the addition of the Delta coronavirus. Although all four genera of Covid can be detected in mammals, alpha-and beta-coronavirus genes are more likely to come from Covid bats, whereas gamma- and delta-coronavirus genes come from avian Covid. There are six coronaviruses known to cause human infection, including alpha

coronaviruses (HCoV-229E and HCoV-NL63), beta coronaviruses (HCoV-OC43 and HCoV-HKU1), SARS-CoV (severe acute respiratory syndrome), and MERS-CoV (Middle East respiratory syndrome) (MERS). SARSCoV2, a novel coronavirus, was discovered after cases were reported in China in late 2019. MERS-

CoV and SARS-CoV-2 have the potential to induce life-threatening symptoms. To successfully infect their host cells, different coronavirus subtypes use different receptors. The numerous forms of coronavirus and their receptors are summarised in the table below [10].

Subfamily	Name	Receptor
alpha-coronavirus	HCoV-229E	aminopeptidase N (APN)
alpha-coronavirus	HCoV-NL63	angiotensin converting enzyme 2 (ACE2)
beta-coronavirus	HCoV-OC43	N-Acetylneurameric acid (Neu5Ac or NANA)
beta-coronavirus	CoV-HKU1	dipeptidyl peptidase 4 (DPP4)
beta-coronavirus	SARS-CoV-1	angiotensin converting enzyme 2 (ACE2)
beta-coronavirus	MERS-CoV	dipeptidyl peptidase 4 (DPP4)
beta-coronavirus	SARS-CoV-2	angiotensin converting enzyme 2 (ACE2)

Fig. 1: Table of different types of coronavirus

Pathogenesis of coronavirus

SARS-CoV-2 enters the human body via attaching to the ACE 2 receptor, which is prevalent in numerous organs and then infects target cells. It accomplishes this by connecting its S glycoprotein (spikes) to the host cell's ACE2 receptor. SARS-CoV-2 spike protein is processed by transmembrane protease-serine 2 (TMPRSS2), which favours spike protein binding to ACE2. A total of 17 spike protein residues interact with 20 ACE2 amino acids, 8 of which establish hydrogen bonds with 13 S residues. These two proteins (TMPRSS2 and ACE2) play a key role in the virus's entrance. The virus penetrates the cell after binding.

SARS-CoV-2 will then release its genetic material in the cytoplasm and be translated in the nuclei after being introduced. For the generation of their proteins and infectious progeny, all viruses rely on the translation machinery of the host cell. In the ER-Golgi intermediate compartment, the translated structural proteins and genomic RNA are assembled into the viral nucleocapsid and envelope, which is then discharged by exocytosis. The virus then spreads to other parts of the body, binds to the ACE 2 receptor on other cells, and repeats the process, producing additional infection.

SARS-CoV-2 and other coronavirus infections have also been linked to the co-receptors DPP4, ANPEP, ENPEP, and TMPRSS2. The other four co-receptors RNA was accumulated in normal lung, mammary gland, liver, prostate gland, thyroid gland, head and neck tissues, small intestine, and kidney tissues, in addition to ACE2 [11-13].

Immune response

In Covid-19 patients, both the innate and adaptive immune systems show changes. IL-6, IL-1, IL-2, IL-8, IL-17, G-CSF, GM-CSF, IP-10, MCP-1, CCL3, and TNF are among the cytokines generated by macrophages. In severe cases of Covid-19, there is also a reduction in CD8+T and B cells and an increase in the CD4/CD8 ratio [14, 15].

Natural products which Inhibits the SARS-COV-2

EGCG

(-)Epigallocatechin Gallate, is a water-soluble flavonoid derived from the Theaceae family's *Camellia sinensis* L [16]. EGCG has anti-oxidant, anti-inflammatory, anti-atherosclerotic, cardio-protective, anti-cancer, anti-obesity, neuroprotective, anti-diabetic, anti-bacterial, and anti-viral properties and is used to treat a variety of ailments [17-19]. In comparison to the other flavonoids present in green tea, EGCG has the highest anti-proliferative potential, and its antioxidant activity is 30 times greater than that of vitamin C and vitamin E [20].

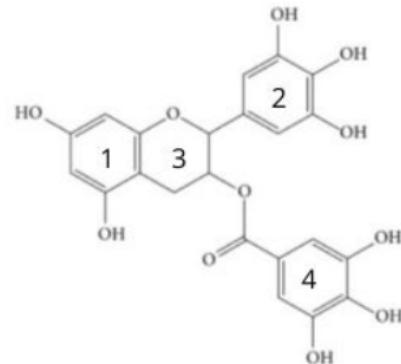


Fig. 2: Basic structure of EGCG (Molecular weight: 458.375, Molecular formula ($C_{22}H_{18}O_{11}$)

EGCG has antiviral characteristics, making it effective against a variety of ssRNA viruses, including:

Dengue

EGCG interacts with virus molecules early in infection and demonstrates antiviral activity directly on virions, producing structural abnormalities and so blocking virus infection [21].

Chikungunya

EGCG can prevent the virus from entering the body, as well as its reproduction and release [22].

PRRSV (Porcine Reproductive and Respiratory Syndrome Virus)

EGCG inhibits PRRSV infection in MARC-145 cells by inhibiting viral receptors or associated PRRSV proteins necessary for infection [23].

Ebola

While EGCG has no effect on the Ebola virus, it does suppress the HSPA5 protein. The Ebola virus employs the HSPA5 protein as a growth factory, but EGCG inhibits it, preventing virus multiplication [24].

HIV (Human Immunodeficiency Syndrome)

EGCG prevents virus entry into target cells by interfering with the interaction between host cell receptors with virus envelope [25].

Influenza A/H1N1 and B/H3N2

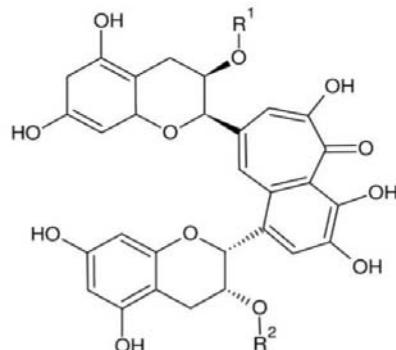
EGCG prevents the acidification of intracellular endosome compartments, which is required for virus-host cell membrane fusion [26].

Even if we talk about the oral bioavailability of EGCG in healthy humans, it is as low as only 0.2-2% of total ingestion, despite its high antiviral potential. This is due to its low stability at pH 7.4, even if we talk about the oral bioavailability of EGCG in healthy humans is as low as only 0.2-2% of total ingestion [27].

Theaflavins

Camellia sinensis L, a member of the Theaceae family, also contains theaflavins. To make black tea, fresh *Camellia sinensis* L leaves are plucked and allowed to dry out in order to trigger biochemical changes in the leaves that produce aroma. The leaves are then subjected to oxidative fermentation (during which theaflavins are generated) before being dried at a high temperature to cease enzyme activity.

It is classified into four types based on which R group it has in its structure: TF, TF2a, TF2b, and TF3.



Compound Name	R	R'
TF1 (Theaflavin)	H	H
TF2a (Theaflavin-3-monogallate)	Galloyl	H
TF2b (Theaflavin-3'-monogallate)	H	Galloyl
TF3 (Theaflavin-3,3'-digallate)	Galloyl	Galloyl

Fig. 3: Basic structure of theaflavins and their classification

Antibacterial, antiviral, hypolipidemic, anti-inflammatory, anti-mutagenicity, and anti-cancer properties are all demonstrated by theaflavins [28-30]. Antioxidant value of the theaflavins is strong, and the antioxidant potential of all four is high.

Theaflavins have a higher anti-oxidant potential than BHT (butylated hydroxytoluene); the order of anti-oxidant potential is TF3>TF2 = TF1>EGCG>TF [31].

Anti-viral effects of theaflavin

HIV (Human immunodeficiency syndrome)

The HIV gp41 protein facilitates fusion between cell lines that express receptors and co-receptors. By attaching to the N-terminal heptad repeats of the gp41 protein, TF3 effectively prevents the development of the gp41 six-helix bundle. The host cell is thus protected against infection [32].

HSV (Herpes simplex virus)

TF3 in combination with acyclovir results in a 21.8 percent reduction in HSV types 1 and 2 strains [33].

Influenza A/H1N1 and B/H3N2

When compared to other flavonoids, theaflavin has a higher antiviral potential (IC50 of 16.21 g/ml). Theaflavins inhibit the influenza virus's RNA-dependent RNA polymerase (RdRP) [34].

HCV (Hepatitis C)

HCV uses the Y-box binding protein-1 and its related proteins to hijack the host particle. TF3 has antiviral effects on these proteins,

preventing the virus from attaching to the host's surface and so preventing infection [35].

TMV (Tobacco Mosaic Virus)

By attaching to the TMV-RNA complex, TFs disrupted the viral replication cycle [36].

The oral bioavailability of Theaflavin in the body is still unknown after multiple trials; however, it is known that it is substantially lower than the oral bioavailability of other polyphenols. Theaflavin's stability is low in alkaline settings (pH 7.4), while it is significantly more stable in acidic ones.

EGCG and theaflavin anti-viral potential against SARS-CoV19

It is apparent that EGCG and Theaflavin decrease viral activity by acting on either the viral protein or the protein that attaches or transfers the viral protein. Let's look at the antiviral properties of these flavonoids in the context of SARS-CoV19.

Inhibition of 3CLpro (chymotrypsin-like protease)

Main protease (M^{pro}), sometimes known as M^{pro} , is a key player in viral replication. PL^{pro} (papain-like proteases) and $3CL^{pro}$ cleave the polyprotein chain into 16 NSPs (non-structural polyproteins), with $3CL^{pro}$ producing 11 of the 16 NSPs created by these proteases.

The IC50 value of EGCG against SARS-CoV19 is 73.2 M, and it inhibits $3CL^{pro}$ by 85 percent. When EGCG is subjected to silico molecular docking, the results show that it interacts with the catalytic residues of 3CL protease with a docking score of 11.7, and that this contact (3CL protease-EGCG) is highly stable.

Theaflavin is more effective than EGCG for inhibiting 3CL^{pro}. TF3 has a higher docking score (10.574) than several antiviral medicines. TF2b has one galloyl group, whereas TF3 has two, allowing them to establish additional hydrogen connections with 3CL^{pro}.

These docking scores and binding to 3CL^{pro} active sites suggest that EGCG and Theaflavins, notably TF3, can easily suppress 3CL^{pro}'s activities, protecting the host from infection [37-39].

Action on RdRP

The enzyme RNA-dependent RNA polymerase (RdRP), also known as RNA replicase, catalyses RNA replication from an RNA template. It is an important protein for all RNA viruses since replication is impossible without it. It's particularly important for RNA viruses since RdRP allows them to replicate without the requirement for a DNA strand. According to computer simulations, EGCG forms a stable complex with RdRP (SARS-CoV-2 RdRP complex), interfering with its functioning. Furthermore, TF interacts with RdRP with a binding energy of 9.11 kcal/mol, interfering with RdRP activities [40].

By preventing the interaction between SARS-CoV19 spike and ACE2 (angiotensin-converting enzyme 2)

The viral infection is started when the SARS-CoV19 spike glycoprotein interacts with ACE2. To inhibit the viral infection,

either the active sites of the viral spike glycoprotein or the ACE2 sites must be hidden.

EGCG binds to the active regions of the SARS-CoV19 spike glycoprotein, blocking it from interacting with ACE2, according to research. Furthermore, the TF3 directly binds to the ACE2, acting as a prophylactic [41, 42].

Inhibition of glucose-regulated proteins (GRP78)

Binding immunoglobulin protein (BiP) or heat shock 70 kDa protein 5 are other names for it. GRP78 is responsible for preventing the unfolding of proteins that have been translocated into the endoplasmic reticulum (ER). GRP78 expresses itself more in stressful situations, making it a good candidate for becoming a viral genome receptor.

GRP78's ATPase activity is inhibited by EGCG, which limits GRP78's ability to operate as a good carrier of the viral genome [43].

It is obvious from the foregoing findings that EGCG and Theaflavins are capable of treating SARS-CoV19 infection and halting SARS-CoV19 proliferation.

However, there is a problem with their stability; both EGCG and Theaflavins are not stable at pH 7.4 (which is the pH of alveoli), and as a result, some Research and development are required to deliver the anti-viral potential of EGCG and Theaflavins.

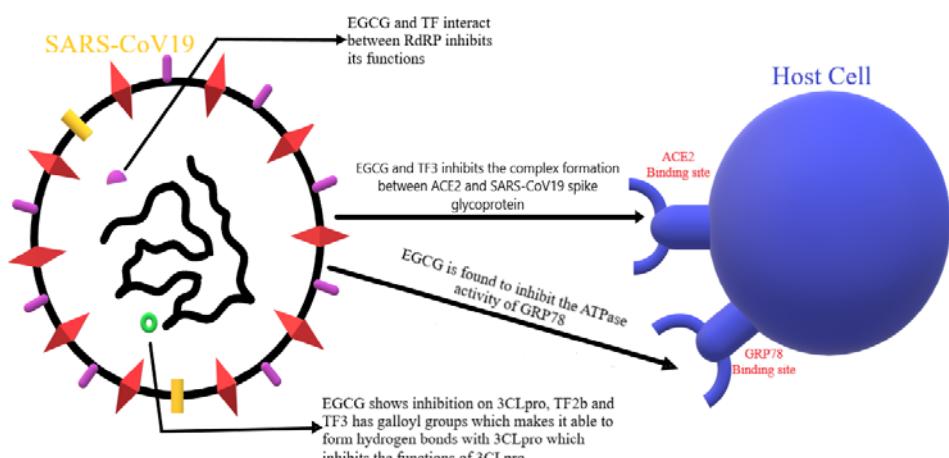


Fig. 4: Effects of Theaflavins and EGCG on SARS-CoV19

Other flavonoids against covid-19

According to a molecular docking research, naringenin, hesperidin and quercetin can bind to M^{pro} by creating H-bonds with the M^{pro} active site amino acids, indicating that naringenin can inhibit SARS-CoV-2 M^{pro} [44, 45].

Hesperetin, linebacker, myricetin, and caflanone have high affinity for S protein, helicase, and ACE-2 receptor, and hence can prevent Covid-19 virus entry [46].

The human TMPRSS2 protease is required for the virus's activation via S protein cleavage. The results of a computer analysis revealed that the flavonoids myricitrin, neohesperidin, naringin, and icariin had a significant binding affinity for TMPRSS2 [47].

Patients with severe COVID-19 have increased plasma levels of GCSF, IP10, MCP1, MIP1A, IL-2, IL-6, IL-7, IL-10, and TNF-, indicating elevated pro-inflammatory cytokine levels. Hesperetin, Naringenin, Fisetin, Chrysanthemum, Quercetin, Apigenin, Luteolin and Caflanone possess potent anti-inflammatory effect [48].

Conclusion and future aspects

Covid-19 instances are increasing, and the virus is mutating, posing a significant threat to humanity. Because there are so many virus receptors in the body, Covid-19 spreads quickly. The virus's action

and dissemination rate is rapidly rising and altering itself as a result of this excess of receptors. Several flavonoids have been shown to reduce or even eliminate the virus's ability to do so. EGCG and Theaflavins, two of these flavonoids, are able to resist covid virus by blocking virus genome binding to ACE-2 receptors and GRP-78 receptors, as well as inhibiting the RdRP protein and 3CLpro, which lowers viral protein. All of these studies suggest that flavonoids can be used to inhibit Covid; however, there is a difficulty with flavonoid stability. Flavonoids are unstable at lungs pH, therefore flavonoids powder cannot be administered to patients directly since it can irritate their airways.

Future characteristics should be completely reliant on the distribution method; the better the delivery mechanism, the more stable it will be and the greater the bioavailability. The flavonoids are particularly compatible with nano-vesicular structures like Spanplastics, and they can readily preserve the flavonoids until they reach the target site. As a result, a nano-vesicular system can readily overcome Flavonoids' detrimental stability effects and prevent the SARS-CoV19 pandemic.

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DATA AVAILABILITY

The original data that support the findings of this study are included in the article.

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AUTHORS CONTRIBUTIONS

Syed Saif Imam proposed the idea and all the other authors have contributed data to the paper.

CONFLICTS OF INTERESTS

The authors confirm that the content of the article has no conflict of interest.

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