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Green Tea Catechins: Role as Antiviral Agents

Rizwana[1], Saamir Akhtar[1], Anita Sondhi[2]*

Abstract

Green Tea Catechins (GTCs) - unarguably the wonder compounds with numerous medicinal properties and health benefits. And most importantly, these benefits include antiviral effects, so significant nowadays in our corona-hit world. The major catechins of green tea are four - epigallocatechin gallate (EGCG), epigallocatechin, epicatechin, and epicatechin-gallate. While each one of these has its own unique properties, EGCG, as per different studies, has been reported to be the most effective catechin showing significant antiviral activity against a broad spectrum of human and animal viruses. The antiviral properties of green tea extracts are manifold and target different areas. These include direct inactivation of the virus particles, prevention of entry into the target cell, inhibition of gene expression, inhibition of protein expression, inhibition of intestinal α-glycosidases that are important for processing glyco-conjugates of viruses, and lowering of proliferation of virus. Furtehrmore, a positive correlation between the antioxidant effects of catechins and their antiviral activities has been suggested. The growing concern about our health and the persistent fight while we are amidst the present coronavirus pandemic makes the inhibitory effect of GTCs a promising area of research. Due to their "relief and rectification" properties, these may be considered as a food supplement to ameliorate the harmful and deadly effects of the virus. The bioavailability of these polyphenols has been shown to be influenced by factors such as temperature, food processing methods, food matrix, and interaction with other compounds. Furthermore, the hydrophilic nature of EGCG molecule limits its bioavailability at the site of action. However, this limitation can be overcome and bioavailability of GTCs can be increased by chemical interventions, such as attachment of fatty acids. These ensure wide availability, and even wider use. The leading objective of this review is to collate, summarize and explain the information available on GTCs, and their effect on various pathogenic viruses in humans and animals. The GTCs surely promise to be an important weapon in our armour to fight corona and other pathogens.

Keywords: Antioxidative, Antiviral, Green tea catechins, Human health, Inhibitory, Polyphenols, Therapeutic

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Introduction

Over the recorded history of the mankind, infectious diseases caused by viruses have seriously threatened human health worldwide. The sad and unmistakable truth is that the viruses are accountable not only for acute infections but also for many chronic infectious diseases, which have played havoc with the health infrastructure many a times. There are surely no shortcuts to deal with the stress, trauma and deaths caused by a variety of viruses, the latest being COVID-19. To prevent the often life-threatening diseases caused by viruses, the discovery of effective antiviral drugs, in addition to vaccine development, is essential.[1]

As any physician will testify, the most common types of infections we come across are viral infections. At the same time, treating this powerful army of viral infections is limited by the accessibility of suitable drugs. Drugs accepted so far, and after years and years of research, have limited applications due to relatively low cure rates, side effects, and the rapid accumulation of drug-resistant mutants.[2] The limited therapeutic applications of the agents, including interferon and nucleotide analogs, have strengthened the need, and hence, search for alternative antiviral agents to treat viral infections.[3-5]

Undoubtedly, tea is one of the most frequently consumed beverages globally, second only to water.[6] Its uses have been cited as early as in China, in 3000 Before Christ or, as some sources suggest, even earlier.[7] Regular consumption has been attributed to various health benefits it offers, including chemo-preventive efficacy. *Camellia sinensis*, used in traditional Chinese medicine, has beneficial properties for humans and animal health, including cardio-protective, anticarcinogenetic, and anti-infective effects. The leaves of plant *C. sinensis* (Green tea) are dried and steamed to avoid fermentation.[8] Polyphenols are around 25–35% of the composition of green tea and offer lots of health benefits. These polyphenolic compounds, also known as catechins, fall under the group of flavones, a subtype of flavonoids.[9] The flavonoids present in green tea have two aromatic rings, A and B, with hydroxyl groups.[10]

The important catechin in green tea is (–) - epigallocatechin gallate (EGCG) [Figure 1], which constitutes about 59% of the overall catechins present in green tea leaves. In addition, the other catechins in green tea are (–)-epigallocatechin (EGC) (19%) [Figure 2], (–)-epicatechin-gallate (ECG) (13.6%) [Figure 3], and (–)-epicatechin (EC) (6.4%) [Figure 4] (Jin, 2013, Tran, 2013; McKay and Blumberg, 2002;) and (+)-catechin [Figure 5].

Many types of infectious diseases caused by various viruses have a considerably detrimental effect on human health and quality of life. Viruses are accountable for not only acute infections but also for many dreadful infectious diseases, for example, the viruses causing Hepatitis (HBV and HCV) play a significant role in chronic hepatitis, liver cirrhosis, and liver carcinoma.[11]

[1]Department of Food Technology, Bhaskaracharya College of Applied Sciences, University of Delhi, New Delhi, India.

[2]Department of Biochemistry, Bhaskaracharya College of Applied Sciences, University of Delhi, New Delhi, India.

Corresponding Author: Anita Sondhi, Department of Biochemistry, Bhaskaracharya College of Applied Sciences, University of Delhi, New Delhi, India. E-mail: anita.sondhi@bcas.du.ac.in

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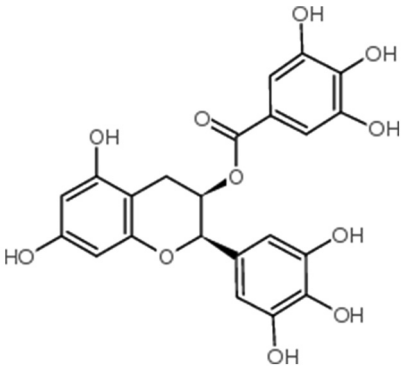
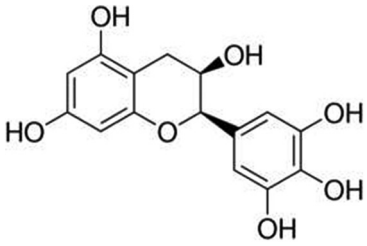


Figure 1: (-)-epigallocatechin gallate (EGCG)



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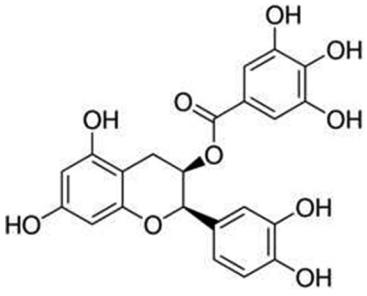

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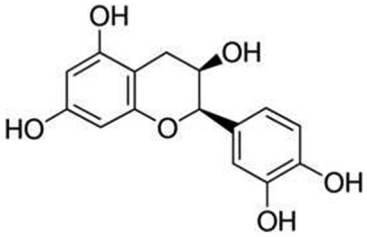

Figure 4: (-)-epicatechin (EC)

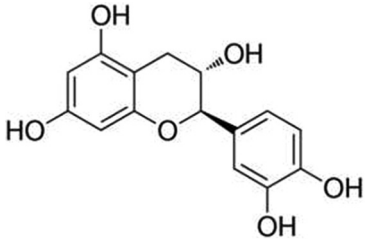

Figure 5: (+)-catechin

The Epstein-Barr virus (EBV) can give rise to a chronic active infection characterized by chronic and recurrent infectious mononucleosis-like symptoms, stomach cancer, nasopharyngeal carcinoma, lung cancer, multiple sclerosis, and even systemic multi-organ involvement.[12]

The human immuno-deficiency virus (HIV) can encroach upon the vital cells in the human immune system and cause the gradual breakdown of the immune system. This lead to a universally dreaded and most suitably named disease - Acquired Immuno-Deficiency Syndrome (AIDS).[13]

Now, as the original cause of the chronic viral infectious diseases is the invasion by the contagious virus; therefore, effective anti-viral treatments are essential. In recent years, green tea catechins (GTCs) have demonstrated inhibitory activities against various viruses, such as human viruses,[3,14-17] livestock viruses,[18,19] fish viruses, and some arboviruses, such as dengue viruses (DENV),[20] Chikungunya virus (CHIKV),[21] and Zika virus (ZIKV).[22]

As is abundantly clear, the Green tea polyphenols (GTPs) are best known for a variety of functions, that include antioxidative,[23] antiproliferative,[24,25] anti-inflammatory, antibacterial,[26] antifungal,[27] and antiviral activities.[28] Evidence shows that green tea is also effective against hypercholesterolemia and hyperglycemia.[29]

GTPs unleash a broad spectrum of activities against different ribonucleic acid (RNA) and deoxyribonucleic acid (DNA) viruses.[30] The antiviral property of polyphenols is due to their antioxidants nature, inhibition of the enzymes involved in viral replication, and their cell membrane disruption. The usage of *in vitro* preparations like isolated aorta has made an invaluable contribution to phytopharmacology[31] with actual results.[32,33]

The list of their beneficial properties is endless. The GTPs also deter viral penetration and binding to cells, triggering the host cell's self-defense, effecting the cell signalling pathways.[34] EGCG has an inhibitory effect on finding access to human umbilical vein endothelial cells, inhibits fibrillogenesis of chicken cystatin[35] protects cells of human retina, vascular permeability and ocular neovascularization[36] prevents tumor blood vessel growth, and protects against the formation of mutations in DNA molecule.

Considering the countless properties of GTCs which can be effectively mobilized in our fight against the incessant attack by viruses, their usefulness can never be in question. But to harness them, we need to be more aware. Hence, the objective of this article is to update information regarding GTPs and enumerate its beneficial effects toward prevention of viral diseases in humans and animals.

Antiviral Effects of Green Tea

Adenovirus

Adenovirus is an icosahedral non-enveloped DNA virus roughly 60–90 nano meters in diameter. Adenovirus infection can lead to cold-like symptoms: sore throat, bronchitis, pneumonia, and pink eye. At any stage of life people can be infected with adenovirus infection. It has also been reported that EGCG at micromolar concentrations reduced the virus titers of adenovirus in two cell infection models and deactivated purified adenovirus.[37]

Adenoviruses (Ads) are involved in various human and animal infections.[38] Sporadic shedding of Ads is one of the symptoms of persistent asymptomatic infection.[39] Ads infect the lining of

the intestine and eyes causing gastroenteritis and conjunctivitis, respectively. They also colonize mucous membranes of urinary and respiratory tracts, and cause other symptoms.[34]

Adenovirus proteases, involved in cancer metastasis, are inhibited by GTCs.[37] Green tea and, in particular, EGCG is efficiently taken up by cells and it inhibits one or more late steps of adenovirus infection.[40]

Antiviral properties of EGCG include direct inactivation of the virus particle, inhibition of intracellular growth *in vitro* and inhibition of the protease adenain.[37,41] Report the anti-viral activity of GTCs against the fowl adenovirus type-4, in the *in vitro* as well as *in vivo* studies.

Hepatitis B Virus (HBV)

Infection with hepatitis viruses is the leading cause of hepatitis in the world. There are five kinds of hepatitis virus: hepatitis A, hepatitis B, hepatitis C, hepatitis D, and hepatitis E. HBV and HCV are the primary cause of chronic liver diseases, such as liver fibrosis, cirrhosis, and hepatocellular carcinoma. HBV is a severe threat to international human public health, as hundreds of millions are infected. Despite vaccination programs, the possibility and potential for outbreaks and epidemic spread cannot be excluded. Unfortunately, the most commonly used medications or treatments for HBV have success rates based on viral genotype and suffer from several limiting after-effects.[42] Therefore, discovery of more effective therapies without after-effects is of great importance.

It is predicted that about 40% of the global human population suffers from the HBV.[43] In Asia, about 5% of the population is chronically infected with HBV, considered endemic.

Catechins are active in several models of inflammatory liver injury. They are often used to treat human liver diseases such as hepatitis C and alcoholic cirrhosis.[44] HBV belongs to the Hepadnavirus family with a 3.2-kb genome of partially double-stranded DNA. In 2008, there was a report regarding the anti-HBV activity of GTCs in HepG2-N10, a stable cell line expressing HBV antigens.[3]

Various concentrations of green tea extracts (GTEs) were found to influence the expression and synthesis of extracellular HBV DNA and HBV antigen. Intracellular replicative intermediates, cDNA and HBV messenger RNA (mRNA) were inhibited with HepG2-N10 cells. Other findings have shown similar results; for example, EGCG could prevent the production of HBV genomic DNA and had a significant role on the expression of two HBV antigens.[45,46]

GTE reveals an overall inhibitory effect on the expression of hepatitis B e antigen (HBe Ag) and hepatitis B surface antigen (HBs Ag). Evidence has shown that hepatitis B e antigen plays a role in viral persistence. It has been suggested that HB e antigen is responsible for chronic effects of HBV by acting as an immune-regulatory protein.[47] Recent studies have shown that GTE had an inhibitory effect on intestinal α-glycosidases that are important for processing glyco-conjugates of viruses.[48]

We found that among five different GTCs, EGCG showed the most substantial inhibition of HBV antigen expression. The mechanism may involve EGCG acting as an antagonist of the farnesoid X receptor alpha (FXRα) and the interaction between EGCG and FXRα downregulating the transcriptional activities of the HBV EnhII/core promoter.

EGCG significantly inhibits replicative intermediates DNA synthesis, reducing circular DNA.[49] According to Pang *et al*. (2014), EGCG exhibits potent anti-HBV action *in vitro*, inhibiting the production of HBs Ag and HBe Ag. Huang *et al*. proposed to reduce the emergence of resistant viruses by combining a new plan of action with other anti-viral drugs.[50]

In 2014, Huang *et al*. found that EGCG could inhibit different genotypes of HBV in immortalized human primary hepatocytes and, DMSO-differentiated Hus-E/2 cells and HA-NTCP-expressing Huh7 cells. Sodium Taurocholate co-transporting polypeptide (NTCP is a receptor of HBV.[50]

Moreover, in the membrane, clathrin-dependent endocytosis of NTCP was induced and directed to protein degradation pathways by EGCG. However, EGCG did not change HBV structures or the expression of genes involved in HBV entry. Recent evidence indicates that host cells can trigger autophagy during infection, a lysosomal degradation mechanism that is important for cell survival. The results of Zhong *et al*. showed that to combat the incomplete autophagy induced by HBV, EGCG can create a microenvironment that is detrimental to HBV replication by altering lysosomal acidification.[51]

Hepatitis C Virus (HCV)

HCV infection is an extreme health hazard around the globe. All over the world, 160 million people are chronically infected with HCV.[52] HCV infection leads to chronic hepatitis, leading to more progressive liver diseases, including cirrhosis, hepatocellular carcinoma, and fibrosis.[30] However, effective therapies are costly, and hence these are out of reach of most of the patients. These are further burdened with after-effects such as anemia appearance and resistance variant, limiting these remedies' effectiveness.[53]

EGCG has been shown to act by inhibiting HCV entry into target cells and prevents cell-to-cell spread between neighboring cells.[54] EGCG inhibits the major HCV NS3/4A serine protease and NS5B polymerase.[55] It was found that EGCG has an inhibitory effect on cell culture-derived particles and the entry of HCV pseudo cells, irrespective of the genotype.[16,56] EGCG also has an inhibitory effect on the replication cycle.[57] It has been indicated or revealed that EGCG cleared the HCV at 50 μM concentrations.[16] In general, green tea gallate catechins are the inhibitors of the HCV.[58]

Influenza Virus (IV)

IV includes the pathogens of the flu outbreak in birds and many mammals, including humans, pigs, horses, whales, seals, bats, etc. The IVs have been classified based on the antigenicity of the nucleocapsid protein into four different categories of IVs: IV A, IV B, IV C, and IV D. Influenza A virus (IAV) is a member of the family of Orthomyxoviridae and has a segmented single-stranded, negative-sense RNA genome. IAV is the primary virus of the flu pandemic because of its high mutation rate. As early as 1949,[59] reported the anti-viral activity of tea extracts against the IV.

Influenza is a very common and acute viral disease that can cause different degrees of systemic symptoms of respiratory failure, and death.[60] Sialidase inhibitors, anti-influenza drugs, and M2 channel blockers[61] are successful if the drug is taken immediately after getting the infection.[62] A need to develop new antiviral drug for therapeutic use has been felt.[63] The ability of the experimental animals to survive the challenge of the IV infection was significantly enhanced when they had been previously treated at a dosage of EGCG at 40 mg/kg body weight.[64]

The first important discussion of the effects of EGCG against influenza A and B viruses was demonstrated in Madin Darby Canine Kidney (MDCK) by Nakayama's research group in 1993. They found that EGCG inhibited the infection of both IAV and influenza B virus. Moreover, EGCG employ agglutination effects on virions and prevented the virus from absorbing the cell surface.[65] The GTE has an inhibitory effect on the replication of IVs by preventing acidification of intracellular compartments, such as endosomes and lysosomes.[66,67]

Hydrolysable tannins obtained from the tea plant inhibited the IV in the early stage of infection.[63] It has been demonstrated that use of catechins for 5 months had an inhibitory effects on IV infection, and had no side effects.[67] Yang *et al*. (2014) compared the *in vitro* anti-viral activity of various components of green tea in IV A and B.[68]

To understand the correlation between the structure and activity of different GTCs,[23] and to check the capabilities to inhibit the replication of viruses, EGCG was found to have a greater extent of inhibition in comparison to ECG and EGC on the activity of both viral genomic RNA synthesis and viral neuraminidase, suggesting the 3-galloyl group of the catechin skeleton was more critical for antiviral activity than the 5'-OH in the trihydroxy benzyl moiety at the 2-position.[68]

Some researchers investigated the inhibitory effects of EGCG analogs, derivatives, and formulations on the IV.[69,70] To prove that the hydroxyl substituents on the A-ring of EGCG played a minor role in anti-IV action, Furuta *et al*. employed deoxy-EGCG, which was made by adding a ketone group at C3.[71] Studies have shown that QR-435, a natural extract from green tea, blocked transmission of IAV H3N2 and provided prophylaxis against H3N2. Furthermore, wearing masks containing QR-435 could prevent H3N2 infection.[69,70]

The derivatives of EGCG (fatty acid esters), especially those with long alkyl chains, exhibited a sharply increased antiviral effect against IAV than natural EGCG.[72] The different nutrient mixtures of natural EGCG have an inhibitory effect on IV and has also been demonstrated by various investigators.[73-75] Some researchers have undertaken clinical trials of EGCG as an IAV restriction factor.[76] One research team discovered a link between IV infection and gargling tea catechin extract, demonstrating that GTCs dramatically reduced the influenza infection incidence in 124 elderly individuals aged 65 and up.[76]

GTCs have been shown to limit IAV replication, with this impact mediated by catechins binding to the active pocket in the viral RNA-dependent RNA polymerase's endonuclease domain. The catechins extract could become an anti-endonuclease herb-based medicine because this enzyme is largely conserved among IAV strains.[77]

HIV

HIV-1 (AIDS) is the etiological agent of AIDS, which belongs to the Lentivirus group of the Retroviridae family. HIV infects CD4+ T-lymphocytes, causing their depletion and hence, the development of immunodeficiency. In 1994, Chang *et al*. reported the anti-HIV activities of polyphenolic catechins for the first time from Chinese green tea.[78]

The researchers isolated EGCG, EC, and ECG from *C. sinensis*. They proved their potential as novel HIV reverse transcriptase (RT) inhibitors. In 1983, Barré-Sinoussi and Luc Montagnier discovered HIV, the AIDS infection.[79] There are two forms of HIV: HIV-1 and HIV-2. HIV-1 was the first virus to be discovered and is still the most common, while HIV-2 is less contagious. Around 12 million people are infected with HIV-2, with a diverse geographical and age distribution. According to the World Health Organization (WHO), around 70 million people have been infected with HIV since the epidemic began. HIV-related diseases have claimed the lives of almost 35 million individuals worldwide.

Globally, there were roughly 36.7 million HIV carriers at the end of 2015.[79] As a result, researching new therapies and looking for new treatments is critical in the fight against AIDS. Significant inroads had been made in anti-HIV therapy and vaccine in the past few years,[80] more than a dozen study groups have worked on tea catechins' anti-HIV properties, primarily anti-HIV-1.

HIV RT is inhibited by EGCG. Chang *et al*. found that three catechins, EC, ECG, and EGCG, have a strong inhibitory effect on HIVRT.[78] The catechins examined were competitive inhibitors of the template-primer and noncompetitive inhibitors of dTTP, according to kinetic analyses.[78] EGCG, acting as an inhibitor of HIVRT, reduced the expression of the HIV p24 antigen in (PBMCs) human peripheral blood mononuclear cells, resulting in RT activity suppression.[15] Lower physiological quantities of EGCG inhibited both HIV-1 and HIV-2 infections, according to a study by Li *et al*.[81] EGCG acts as a RT inhibitor of HIV-1 infection, decreasing the p24 antigen concentration.[81]

GCG suppresses HIV-1 by directly interacting with the D-1 domain of CD4 and the pocket that binds gp120.[40] In the presence of EGCG, viral transcription is inhibited by a decrease in mRNA.[82] In addition, EGCG has been found to suppress the HIV-1 integrase protein.[83] HIV infection causes severe consequences. HIV infection causes serious consequences that damage the central nervous system.[84] Because of its simple structure and ability to penetrate the blood-brain barrier, EGCG and EC are possibilities for treating neurological consequences of HIV infection.[85]

Semen-derived enhancer of virus infection (SEVI) is a fibrillar structure that collects virions and directs them to their destinations in HIV-1 sexual infection. By forming and degrading complexes, EGCG can reduce SEVI activity.[86,87] Using 47 fresh human semen samples, Hartjen *et al*.[88] corroborated and expanded the findings of Hauber *et al*.

They also observed a semen-independent inhibition of HIV infectivity. In the absence of semen, the inhibition rate of HIV infectivity reached 88.5% after treatment with 0.4 mM EGCG. According to the findings, EGCG could be an alternate medication for reducing HIV transmission through sexual contact.

Bovine Coronavirus (BCV)

BCV is one of the pathogens for diarrhoea in livestock, which often results in tremendous loss of life and livelihood (Traven *et al*. 2001).[89] GTPs have a great potential for the treatment of BCV infection in farm animals. The antiviral activity of EGCG involves S1 proteins of BCV. EGCG inhibits BCV more efficiently in the bovine intestinal tract, where the temperature of 37°C is appropriate for the anti-viral efficacy of EGCG against BCV.

EBV

EBV is a human herpesvirus that causes mononucleosis by infecting human B-lymphocytes (B-cells).[90] EGCG regulates the expression of EBV lytic proteins such as EA-D, Zta, and Rta[91] EGCG directly inhibits

the EBV's immediate-early gene before EBV-encodes polymerase and causes the arrest of the EBV lytic cascade. EGCG arrests epidermal growth factor-stimulated at the mid G1 phase of breast epithelial cells and prevents cells from entering the S phase. EGCG may regulate EBV immediate-early gene.[92] EGCG inhibits the phosphorylation and activation of extracellular signal-regulated kinase 1/2 (ERK1/2), which effectively inhibits constitutive EBV infection at the gene transcription, DNA, and protein levels.[64] Through EBV-induced alterations in B-cells, EGCG suppresses EBV infection.[93]

Enterovirus 71 (EV-71)

EV-71 belongs to the family Picornaviridae, having a non-enveloped RNA genome causing outbreaks occasionally worldwide.[94] EGCG and ECG inhibit EV-71 replication and the formation of infectious progeny virions. EGCG inhibits EV-71 infection by decreasing oxidative stress associated with the infection and preventing increased EV-71 replications in G6PD-deficient cells.[95] It has been hypothesised that the presence of the gallate group and the trihydroxy-B ring, both of which have free radical scavenging action, is responsible for EGCG and ECG's strong antioxidant effect against EV-71 infections. As a result, a positive relationship between catechins' antioxidant benefits and their anti-viral activity has been proposed.[95]

Herpes Simplex Virus (HSV)

Herpes simplex virus (HSV) is one of the most common widespread human infectious diseases causing genital infection with type 2 HSV (HSV-2) or oral infection with type 1 HSV (HSV-1).[96] Herpes simplex, a viral skin disorder, is caused by infection with HSV-2 or HSV-1. Both HSV-1 and HSV-2 are Herpesviruses with enclosed viruses that have a relatively large double-stranded, linear DNA genome. HSV-1, which is spread through mouth-to-mouth contact, causes genital herpes and cold sores. The most common way for HSV-2 to spread is through sexual contact, which usually results in genital herpes.[97]

Lyu *et al*. discovered that GTCs have anti-HSV action in 2005.[17] EC, ECG, EGC, and EGCG were revealed to have strong anti-HSV action among the 18 flavonoids studied.[17] Following that, research revealed that EGCG had a stronger anti-HSV action than the other GTCs studied, causing infectious clinical isolates of HSV-1 and HSV-2 to lose their ability to infect.[98] The data also showed that the inactivation of the virus occurred because of a direct destructive effect of EGCG on the HSV-1 virions.[98] Another study from same group found that EGCG digallate dimers could inactivate HSV and could be turned into more effective HSV antiviral medicines.[99]

EGCG operates its antiviral activity through oxidation and dimerization by oxidative reactions, which disrupt the HSV envelope.[100] This interruption reduces the spread of HSV *in vivo*.[99] EGCG is stable at vaginal pH and shows as a candidate for use as a topical microbicide to trim down HSV transmission. EGCG also potentially interrupts the synergistic association between the HSV and HIV infection, directly affecting the virion itself.[98]

Prodelphinidin B-2 3'-O-gallate obscured the HSV-2 reproduction in Vero cell without considerable adverse effects on the growth and cell viability.[101] EGCG modified with palmitate enhanced the activity of EGCG as a promising anti-viral agent against HSV-1 infection[96] and lipophilic EGCG is an effective treatment against HSV as a topical application.[102] Furthermore, dimers of EGCG inactivate HSV-1 and HSV-2 more successfully between pH 4.0 and 6.6 than the monomer of EGCG. This mechanism may be more effective in reducing the spread of HSV *in vivo* because predilection sites of HSV are the skin and vagina, where pH is considerably low.[99]

An intriguing study looking into the cause for EGCG's broad antiviral effect discovered that it competed with virion surface proteins to prevent HSV-1 from attaching to heparan sulphate.[56] Furthermore, it was shown that EGCG showed its broad-spectrum anti-viral activities on many other viruses, including HCV, IAV, murine cytomegalovirus, adenovirus, vaccinia virus, vesicular stomatitis virus, and reovirus. This activity was likely due to a same mechanism: it prevented the virus from interacting with heparan sulphate or sialic acid.[56]

Feline Calicivirus A Surrogate of Norovirus and Other Virus Infections

Norovirus fits into the family of Caliciviridae, which is the basis for the outbreak of gastroenteritis in humans and is considered a major cause of food-borne pathogens worldwide and associated with severe childhood diarrhea.[103] The reasons are generally minor and self-limiting, with symptoms lasting 24–48 h. Children can die from chronic, recurring infections.[103] Every year, 21 million instances occur, with 800 fatalities.[104] Green tea's hydrolyzable tannin reduces norovirus burden by four or more log10.[105] Catechin is also active against the FCV, which is a norovirus surrogate. Among the catechins studied, EGCG had the most efficient antiviral activity with a half-effective concentration (EC_{50}) of 12 mg/ml and comparatively low cytotoxicity with a CC50 of 320 mg/ml.[106]

Human Papillomavirus (HPV)

Catechin lotions and creams prepared from GTE have been shown to hinder the HPV at concentrations from 160 to 360 μM.[107]

Human T-cell lymphotropic virus type-1 (HTLV-1)

Human T-cell leukemia caused by HTLV-1 may also be cured with EGCG and GTE as a whole.[108] Green tea is reported to reduce the HTLV-1 provirus in peripheral blood lymphocytes in the HTLV-1 carrier,[109] which downregulates the protein expression of an anti-apoptotic member.[110] Recent research has discovered that (−)-EGCG [Figure 1] is a major norovirus-fighting chemical.[111]

CHIKV Infection

Chikungunya fever is caused by an alphavirus which is spread by mosquitos called CHIKV. The disease is distinguised by a sudden onset of fever, headache, malaise, arthralgia or arthritis, myalgia, and lower back pain.[112,113] After the acute phase, polyarthritis can be recurrent. It may persist for several years after infection, a severe public health issue of concern. Aedes albopictus, the mosquito, inhabits temperate regions, including Europe and the United States of America,[114] documented in the Caribbean as well.[115,116] This disease has neither a vaccination nor a treatment. Recent studies show that the main components of green tea, catechin, and EGCG inhibit virus CHIKV infection.[21]

Ebola Virus (EBOV)

The EBOV causes hemorrhagic fever and is a highly fatal disease. 2014–2016 WHO statistics showed that the EBOV outbreak of cases

in West Africa had a high fatality rate of 28%-75%.[117] Reid *et al*. studied a host chaperon protein, a type of heat shock protein (HSP) S5, as an important target for therapy against EBOV infection. They found that EGCG, as an inhibitor of HSPS5, reduced the production of new viruses through its action on HSPS5.[118]

EVs and Rotaviruses

A series of intestinal symptoms are seen in infection by EVs and rotaviruses. EV-71 is the major disease causing pathogen of hand, foot, and mouth disease. In addition, EV-71 can lead to diarrhea, severe neurological symptoms, and rashes. EV-71 has done great harm to infants' health in both underdeveloped and developing countries. Studies have shown that ECGC from green tea inhibits EVs and rotaviruses in cultured rhesus monkey kidney cells by interfering with virus adsorption.[119]

There is substantial evidence for an anti-EV function of GTCs.[95] The authors found that the proliferation of EV71 was lowered by 95%, after treatment with gallocatechin gallate (GCG) and EGCG and suggested that the inhibitory effects were related to the reduced reactive oxygen species (ROS) generation.[95]

HTLV-1

Adult T-cell leukemia (ATL) is an aggressive T-cell malignancy caused by a HTLV-1 infection. In thirty years since HTLV-1 was discovered, ATL tends to yield poor results, and in terms of cure rates, little progress has been made.[119,120] As a result, novel medicines that target particular molecules and the use of anti-HIV medications should be encouraged.[117] Two groups separately contributed to the discovery of EGCG as an antiviral drug and discovered that it inhibited HTLV-I pX and Tax gene expression.[10]

Arboviruses

An arbovirus is a group of viruses transmitted by insects, most commonly mosquitoes and ticks, sucking blood for nutrients.[121] The common signs of infection with arboviruses are fever and headache. Severe patients present symptoms of encephalitis and hemorrhagic fever.[122] The infections caused by different arboviruses, including tick-borne encephalitis virus (TBEV), DENV, West Nile virus, Japanese encephalitis virus (JEV), and new outbreaks of ZIKV and CHIKV in Latin America, are severe health hazards, especially in tropical and subtropical countries.[121]

Molecular docking methods have proposed that EGCG can dock in the same binding domain of different E proteins from TBEV, DENV, and JEV.[20] CHIKV, an alphavirus, is transmitted by mosquitoes and causes chikungunya fever in humans. Studies have also shown the inhibitory effects of EGCG on CHIKV *in vitro* using a CHIKV-m Cherry-490 infection model. Furthermore, they discovered that EGCG was effective in preventing CHIKV from accessing target cells and had a minimal influence on CHIKV replication.[21]

ZIKV is a mosquito-borne virus with a single-stranded RNA genome that belongs to the Flaviviridae family. ZIKV has expanded swiftly over the world since its outbreak in Brazil in 2015.[123] EGCG showed antiviral activities against ZIKV, according to a study from Carneiro *et al*. in 2016.[22] This group has provided evidence for the anti-viral role of EGCG using Vero E6 cells and two strains of ZIKV, namely, MR766 and ZIKVBR. The underlying process was also investigated. EGCG had no effect on the expression of viral invasion-related cell receptors. As a result, it's thought that EGCG and the viral envelope had a direct interaction, leading to the destruction of ZIKV virions' structure.

Toxicity of GTPs

A huge number of physiologically functional foods are comprised of plant polyphenols. Their antioxidative activities have been intensively studied for an extended period and proposed to have effective health promotional and disease preventive effects.

GTPs possess marked antioxidative properties and versatile, beneficial functions, including anti-inflammation and cancer prevention. On the other hand, some investigators have uncovered their toxicity at high doses, presumably due to pro-oxidative properties. For instance, both the experimental animal studies and epidemiological surveys have demonstrated that GTPs may cause hepatotoxicity.

It was recently shown that diets that contain high doses (0.5–1%) of a GTPs deteriorated dextran sodium sulfate (DSS)-induced intestinal inflammation and carcinogenesis. In addition, colitis model mice fed a 1% green tea polyphenol exhibited signs of nephrotoxicity, as stipulated by alteration of serum creatinine level. This diet also increased thio-barbituric acid-reactive substances, a dependable marker of oxidative damage, in both kidneys and liver, even in normal mice. Concurrently, the expression levels of antioxidant enzymes and HSPs were diminished in colitis and normal mice.

Intriguingly, GTPs at 0.01% and 0.1% showed hepatoprotective activities, that is, they remarkably suppressed DSS-increased serum glutamate oxaloacetate transaminase and serum glutamate pyruvate transaminase levels. Moreover, these diets remarkably restored DSS-down-regulated expressions of heme oxygenase-1 and HSP70 in livers and kidneys [Figure 6].

Low and medium doses of GTPs are favourable in colitis model mice, detrimental side-effects may emerge with high doses.[124]

Green tea also seems to have antidiabetic and antiobesity properties.[125] Based on its potential antiobesity effects, green tea has been marketed during recent years as a herbal supplementation for the control of body weight. Unfortunately, some of the reports of adverse effects, mainly hepatitis, associated with the consumption of green tea preparations have been published. In April 2003, the producer of Exolise **(**Arkopharma, Carros, France), a GTE containing high EGCG levels and marketed it as a weight-loss supplement, withdrew this product from the markets due to thirteen cases of liver damage due to its consumption.[126]

The same product was also pulled out from the Spanish markets because of other hepatotoxicity cases. Since then, much more attention has been given to the possible hepato-toxic effects of green tea. Thirty-four cases of hepatitis following the use of preparations that contain green tea were retrieved from Medline between 1999 and October 2008[11-35] 6 cases were men (27–45-years-old) and 28 women (19–69-years-old).[44,127-150]

Even though green tea products are used for their antioxidant properties, it is now recognized that they possess both antioxidant and pro-oxidant properties. Depending on the conditions, one or the other may predominate.[151] Many phytochemicals have this dual nature.[152] The balance between antioxidant and pro-oxidant activity is vital in maintaining healthy biological systems. Any imbalance can disturb redox homeostasis and lead to redox stress and toxicity.

The human body needs exogenous antioxidants to maintain normal homeostasis and derives them mainly from naturally

occurring phytochemicals present in fruits and vegetables. However, while these naturally occurring phytochemicals act as antioxidants in physiological dietary doses, they can exhibit pro-oxidant activities in large, pharmacological doses or the presence of metal ions. Under those conditions, these same phytochemicals can produce ROS and lead to redox stress.

EGCG was shown to exhibit pro-oxidant activity, produce hydrogen peroxide and ROS, and lead to oxidative stress and *in vitro* cytotoxicity, cancer cells being more sensitive than usual.[153] EGCG was also shown to cause protein carbonylation and form covalent cysteinyl adducts with proteins.[154] These pro-oxidant mechanisms may affect redox-dependent cellular events and cause toxicity.

Among 1414 patients enrolled in the United States Drug-Induced Liver Injury Network who underwent formal causality assessment, 40 cases (3%) were attributed to green tea, 202 to dietary supplements without green tea, and 1142 to conventional drugs.

Patients with green tea-associated liver injury ranged from 17–69 years (median = 40) and developed symptoms 15–448 days (median = 72) after starting the implicated agent. The liver injury was typically hepatocellular (95%) with marked serum amino-transferase elevations and only modest increases in alkaline phosphatase. Most patients were jaundiced (83%) and symptomatic (88%). The course was judged as severe in 14 patients (35%), necessitating liver transplantation in 3 (8%), but rarely resulting in chronic injury (3%). In three instances, injury recurred upon re-exposure to green tea with similar clinical features but a shorter time to onset.[157]

Effect of GTPs on COVID-19

COVID-19 is a viral infection that affects the epithelial cells of the respiratory system and causes inflammation of the mucosal membrane. This leads to alveolar damage and eventually pneumonia. It is caused by severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2), commonly known as novel Coronavirus (CoV), a positive-sense single-stranded RNA virus. Earlier, coronaviruses have been reported to cause SARS and the Middle East respiratory syndrome).[158]

Among the drugs being tested in clinical trials, hydroxychloroquine, favipiravir, remdesivir, and lopinavir/ritonavir have gathered much attention.[159] Several other antiviral drugs and new chemical molecules are also being tested for treatment against CoV. A few dietary molecules with previously established antiviral activities are also among the candidates evaluated for COVID-19 treatment.

Polyphenols inhibiting the life cycle of CoVs bring forth a ray of hope in the use of polyphenolic compounds. The interest shown by researchers worldwide has envisioned green tea as a beverage with functional properties. These compounds present in high concentrations in Green Tea could serve as a prophylactic measure in preventing and treating the COVID-19 virus. EGCG as a potentially safe, natural supplement to counteract hyper-inflammation seen in COVID-19 provides encouraging data.[160]

The inhibitory effect of EGCG on CoV replication provides stimulating data to consider this functional food as a food supplement to ameliorate the infection's harmful and deadly effects that have affected millions all over the world.[161]

EGCG has been tested for its antiviral activity against several viruses and was found to be a very potential treatment option over man-made chemical drugs. It is recognized as a versatile and diverse bioactive molecule exhibiting antitumorigenic, anti-inflammatory, antibacterial, antioxidative, and antiproliferative properties in addition to its antiviral effects.[8]

Bioavailability of Polyphenols

The term "bioavailability" was initially used in pharmacology to define the concept of "rate and extent to which the drug reaches its target site." Although several definitions of bioavailability have been suggested, the most appropriate still seems to be that it is a fraction of an ingested nutrient or a compound that reaches the systemic circulation and the particular sites where it can exert and apply its biological action.[162] In other words, its simply means how much of the ingested quantity of the polyphenols can exert its beneficial effects in target tissues.

To establish conclusive evidence for the efficacy of polyphenols in disease prevention and human health improvement, it is necessary to determine the distribution of these compounds in our diets, estimate their contents in each food, and identify which of the hundreds of existing polyphenols are likely to provide the most remarkable effects in the context of preventive nutrition. Finally, it is necessary to know the bio-availability of polyphenols and their metabolites to evaluate their biological activity in target tissues.[162]

Main Factors Affecting the Bio-availability of the Polyphenols

Bio-availability studies are challenging since several potentially affecting factors exist, they are illustrated in Table 1. These factors may affect bio-availability directly or by decreasing polyphenol content in food.

EGCG is a four-ring structure that is highly soluble in water and not soluble in hydrophobic media. The hydrophilic nature of this molecule limits its bioavailability at the site of action. Studies have shown that lipophilic derivatives of EGCG have a tremendously high antiviral activity in comparison to the parent molecule.[163] EGCG has been reported to be potent virus inhibitor among the natural catechins with the 5'OH and 3-galloyl group playing a crucial role for the virus inhibition activity and the antiviral capability is further enhanced by the attachment of fatty acids to EGCG against a broad spectrum of viruses.[164]

How to Increase the Bioavailability of Polyphenols

Technological methods, such as vegetable homogenization, may improve polyphenol bioavailability by changing the dietary matrix, as has been proven for lycopene and -carotene, two important carotenoids. Tomato puree and paste have been found to be more bioavailable sources of lycopene than raw tomatoes.[162]

Conclusion

Undoubtedly, green tea gets universal thumbs up from various scientific papers scribbled over the past many decades by researchers and scientists. We have shown, backed by various studies, that GTPs are famous, and not without reason, for their various biological and pharmacological activities, including antioxidative, antiproliferative, anti-inflammatory, antibacterial,

Table 1: Main factor affecting the bioavailability of dietary polyphenols in humans

External factors	*Environmental factors (i.e., sun exposure, degree of ripeness); food availability*
Food processing related factors	Thermal treatments; homogenization; liophylization; cooking and methods of culinary preparation; storage
Food related factors	Food matrix; presence of positive or negative effectors of absorption (*i.e*., fat, fiber)
Interaction with other compounds	Bonds with proteins (*i.e*., albumin) or with polyphenols with similar mechanism of absorption
Polyphenols related factors	Chemical structure; concentration in food; amount introduced
Host related factors	Intestinal factors (*i.e*., enzyme activity; intestinal transit time; colonic microflora). Systemic factors (*i.e*., gender and age; disorders and/or pathologies; genetics; physiological condition)

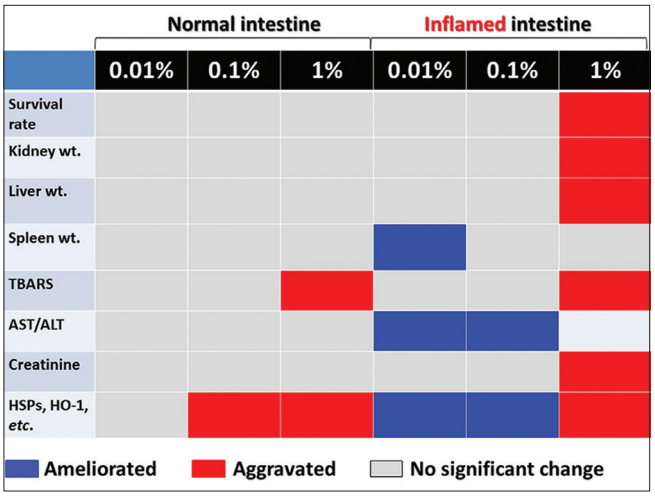

Figure 6: Summary of results of experiments on effects of low medium and high doses of GTPs on large intestine, liver, and kidneys of ICR mice. Summarized from Refs,[155,156] TRABS: Thiobarbituric acid reactive substances, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, HSP: Heat shock protein, HO-1: Heme oxygenase-1

antifungal, and antiviral activities. At the same time, some studies have also reported adverse effects, mainly hepatitis, associated with the consumption of green tea preparations. That surely can not be ignored. However, with benefits far exceeding the negatives, the value of GTCs in our fight against viruses can never be overlooked. However, while immediate deployment of GTCs, backed by so many studies, in this never-ending battle appears to be the need of the hour, at the same time, to promote green tea as a therapeutic, some more human-based studies will go a long way toward addressing these issues.

It is important to emphasise that the inhibitory effect of EGCG on the replication of coronavirus provides a stimulating data to consider this functional food as a food supplement to ameliorate the harmful and deadly effects of the infection that has adversely affected millions all over the world.

As small compounds with broad antiviral activity, catechins like EGCG and also, the catechins that can be chemically modified to increase their bio-availability, need to be looked into in detail and may be used as a reference point to further develop effective antiviral drugs. Furthermore, *in vivo* and clinical studies are much needed to look for cheap and effective ways to treat viral infections.

This fight with viruses is a battle in continuity. Newer and newer weapons will be needed each time when a crisis like the present one unfolds. With a potent weapon like GTCs already at our disposal, we must act swiftly. Spread the message, promote the use, and take the sting out of the viruses that plague the world.

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Conflict of Interest

The authors declare no potential conflicts of interest with respect to research, authorship, and/or publication of this article.

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