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Review Article

Therapeutic Potential of Natural Catechins in Antiviral Activity

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Abstract

Natural compounds have been discovered to be effective in many disease treatments. Among these compounds are epigallocatechin-3-gallate (EGCG) and epicatechin-3-gallate (ECG), two abundant polyphenolic catechins in green tea. They have been found to be able to interfere with many disease-related biochemical processes *in vitro*. They are capable of suppressing inflammation, tumor growth, bacterial infection, and virus infection. Thus, EGCG and ECG have drawn great attention on the potential effects on disease prevention and treatment of carcinogenic, obesity, diabetic, and Alzheimer's diseases. In this review, the potential of EGCG and ECG on anti-viral infection is elucidated in detail with an overview of research achievements in this field. The highlight will provide in depth knowledge on new drug discovery and contribute to the design and development of novel anti-virus agents.

INTRODUCTION

Current strategies for the treatment of various viral infections highly depend upon the virus type. In recent years, considerable progress has been made in the drug development against virus infections. For instance, AIDS patients can receive combinative therapeutic drugs to inhibit HIV reverse transcriptase and protease activities, so that viral load in the blood and lymphoid tissues can be controlled to an undetectable level. This development has led to a significant improvement in the health and life span of HIV-1infected patients. However, these drugs are toxic and extremely expensive. It is reported that the cost incurred in AIDS treatment is not affordable to 90% of HIV infected patients [1]. The average yearly cost of AIDS therapy and the related health care of affected patients in the USA can run as high as $22,000 [1,2]. Moreover, the emergence of drug resistance further complicates the situation. Therefore, a search for new, effective, and affordable anti-HIV agents became a necessity.

Natural product extracts such as plants have low toxicity, minor side-effects, and they are more cost-effective than chemical drugs. Betulinic acid-like compounds extracted from plants are one example of such extracts that have been reported to possess anti-HIV activity [3]. The betulinic acid-like compound can be isolated from the Chinese herb *Syzygium claviflorum* [3]. Derived from this compound is an anti-HIV drug called Bevirimat. It inhibits viral maturation [4]. Preclinical studies demonstrated that Bevirimat retains nanomolar inhibitory activity against drug resistant HIV strains. There was no evidence of the virus developing drug resistance against Bevirimat [5]. Other therapeutic compounds from plants are catechin components. The evergreen plant *Camellia sinensis* produces green tea that maintains its original composition of catechin [6]. Thus, green tea has gained considerable attention as an agent that could reduce the risk of a number of diseases. The natural catechin components in green tea are epigallocatechin-3-gallate (EGCG), epicatechin-3-gallate (ECG), epigallocatechin (EGC), and epicatechin. They have been found to be able to interfere with many disease-related biochemical processes *in vitro* [7,8]. The concentration of the four catechins in a cup of tea is estimated to be approximately one mg per ml, depending on the tea plant, growing environment, manufacturing conditions, and the size of the tea leaves [9,10]. Among the four catechins, EGCG and ECG are the two most abundant catechins in green tea, with EGCG taking up approximately 50% of the total amount of catechins in green tea [11]. EGCG and ECG are also the most effective on suppressing inflammation, tumor growth, bacterial infection, and virus infection both *in vitro* and *in vivo* [12]. They are capable of anti-oxidative, anti-carcinogenic, anti-obesity, anti-diabetic, anti-Alzheimer's disease, and anti-viral activities [13,14] and can even serve as anticancer chemopreventive agents. In addition, they can even provide pronounced cardiovascular and metabolic health benefits [15].

This review focuses on the therapeutic potential of natural catechins for antiviral infections, and highlights the mechanisms of these compounds against viral infection. Figure 1 shows the chemical structure and molecular weight of catechin, ECG, and

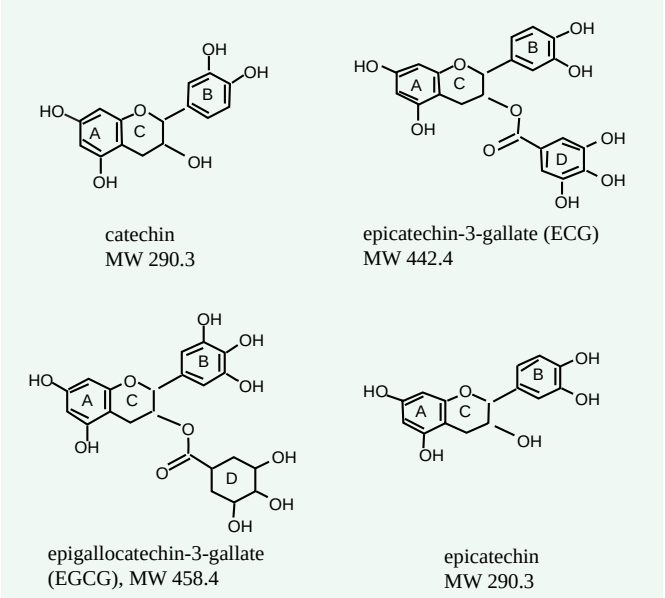

Figure 1 Chemical structure and molecular weight of catechin, ECG, EGCG, and epicatechin.

EGCG. It is the ester of epigallocatechol and gallic acid. The 3-galloyl group plays a critical role in the functional expression of inhibitory effects [16]. The updated information about the therapeutic effect of natural catechins on viral infection may improve the use of catechins and help design novel antiviral drugs.

Anti-HIV infection

AIDS (acquired immunodeficiency syndrome) is a set of symptoms and infections caused by the human immunodeficiency virus (HIV) [17]. HIV-associated reverse transcriptase has been considered as one of the targets for AIDS prevention and treatment because reverse transcriptase is one of the key enzymes in HIV replication. However, most reverse transcriptase inhibitors are toxic and can inhibit cellular DNA polymerases [10,18]. This side effect urged scientists to develop more selective but less toxic medicines for antiviral treatment. Evidence for the anti-viral potential of catechins in green tea has been provided by numerous experimental studies. In 1990, it was reported that the main ingredients of tea catechins EGCG and ECG had strong and selective inhibitory effects on the activity of HIV reverse transcriptase. EGCG and ECG possess gallate ester moieties at the 3 hydroxyl position of the C ring, which could be a key structure for antiviral activity (Figure 1) [8].

The EGCG and ECG, purified from the tea plant, inhibited purified HIV reverse transcriptase much more effectively than they inhibited purified DNA polymerases, as evidently proved by the inhibition constants measured in biochemical assay [19]. These *in vitro* studies also demonstrated that the concentration required for a 50% inhibition of HIV reverse transcriptase (IC_{50}) was approximately 0.045 μM with K_i value of 2.8 nM [16]. In addition, the results also indicated that both EGCG and ECG are strong inhibitors, especially for HIV-reverse transcriptase. The potential inhibitory efficacy of HIV infection and replication by EGCG in cell culture was reported for the first time in 2002. Fassina and co-works demonstrated that EGCG dose-dependently blocked HIV infection, and 100% inhibition was achieved with 50 μM of EGCG in peripheral blood lymphocyte cultures [18]. Since this study, green tea extracts began to be considered as potential inhibitors of HIV infection in anti-HIV therapy. The power of EGCG on anti-HIV infection is confirmed by Hauber and his co-workers as well [20]. It seems like catechins may help reduce viral load [21]. However, the anti-HIV activity of catechins from green tea has yet to be confirmed in live human trials.

Anti-influenza virus infection

Influenza A virus infection is one of the most common infections of the respiratory tract. It causes pandemic and seasonal diseases and leads to severe mortality in humans and animals. The human influenza caused by this subtype H5N1 of the virus had a high case fatality of 54% [22]. Despite annual updates of flu shots in recent years, vaccines are often ineffective because of the frequent antigenic drift in this RNA virus.

The inhibition effect of EGCG on influenza A and influenza B virus was observed by Nakayama group using electron microscope and haemagglutination assay [19]. Their experimental results revealed that EGCG inhibited the infectivity of influenza A and influenza B virus in Madin-Darby canine kidney (MDCK) cells by binding to the haemagglutinin envelop glycoproteins of influenza virus, and thus prevented the virus from adsorbing to MDCK cells [19]. It was found that EGCG and ECG suppressed the viral RNA synthesis and the release of newly made influenza virus particles from infected cells [23]. Jariwalla and his co-workers have developed a naturally occurring nutrient mixture (NM) to evaluate the effect of NM on human influenza A virus subtype H1N1 infection [24]. This NM contains lysine, poline, ascorbic acid, green tea extract, N-acetyl cysteine, and other micro nutrients. The addition of NM to Vero and MDCK cells post infection induced the inhibition of viral nucleoprotein production in infected cells. Ling and his co-workers orally administrated BALB/c mice with EGCG at varied doses for 5 days. On the 3rd day of the treatment, the mice were infected with influenza A virus. EGCG at 40 mg/kg per day dramatically improved the survival rate of the experimental animals, and also decreased virus replication and the mitigation of viral pneumonia in the lungs [25].

There are at least three mechanisms involved in cell death: apoptosis, necrosis, and reactive oxygen damage. Ling and his co-workers found that 20 nmol/L of EGCG can significantly suppress reactive oxygen species level in MDCK cells following influenza A infection [26]. It is impressive that epicatechin and EGCG also target the brain-derived neurotrophic factor (BDNF) and its precursor pro-BDNF signaling pathways. The simpler structure and efficient blood-brain barrier penetration makes epicatechin to be an effective therapeutic candidate for the treatment of neurological complications of HIV infection [27]. 50% effective inhibition concentrations of EGCG, ECG, and EGC for influenza A virus were 22-28, 22-40, and 309-318 μM, respectively [23].

Anti-hepatitis virus infection

Hepatitis B (HBV) is a major cause of liver disease worldwide and a common coinfection in HIV-infected patients, causing

cirrhosis and liver cancer [28,29]. In the U.S., about 1.25 million people are chronically infected with hepatitis B virus (HBV). About 350 million people are estimated to be chronically infected, and 15% to 40% of those people are at risk of developing cirrhosis and/or hepatocellular carcinoma (HCC) [30]. There are currently a number of agents approved for use against HBV. However, the low efficacy, the side-effects, and resistance to HBV mutations of the drugs have encouraged the development of novel therapeutic agents for HBV treatment [31]. The efficacies of green tea extract and the principal component of green tea extract, EGCG, against HBV in a stably expressed HBV cell line have been examined. The experimental results demonstrated that the treatment of green tea extract and/or EGCG inhibited both HBV markers HBsAg and HBeAg in the culture medium in a dose-dependent manner. The IC_{50} of green tea extract against production of HBsAg and HBeAg were 5.02 and 5.68 μg/ml in culture cells tested. In addition, treatment of the green tea extract at a concentration of 40 μg/ml for six days dramatically inhibited the production of the extracellular HBV DNA and nuclear covalent closed circular DNA in the cells. The founding suggests that green tea extract has the potential to become an anti-HBV infection agent [32]. At a 50% effective concentration (EC(50)) of EGCG of 17.9 μM, hepatitis C virus (HCV) infection was also considerably suppressed. It is clear that EGCG suppresses both HCV entry and RNA replication steps in this type of virus cycle [33]. The observation is consistent with findings that EGCG inhibits HCV infectivity by more than 90% at HCV entry step [34,35].

Anti-HTLV-1 infection

Human T-cell lymphotrophic virus type I (HTLV-1) is a retrovirus and is associated with adult T-cell leukemia. It was estimated that this virus has infected 12 to 25 million people worldwide [36]. It causes acute T-cell leukemia (ATL) and is the first human retrovirus to be isolated [37]. Although only 5% of people with HTLV-1 would develop ATL after 30-40 years of latency period, treatments against ATL are not very effective [38,39]. Thus, the effect of EGCG on cells infected with HTLV-1 has been investigated. EGCG induces apoptosis in HTLV-I-infected and non-infected cells. EGCG can significantly inhibit cell proliferation. The IC_{50} values differ from cell types. At 96 h of treatment with EGCG, cytotoxicity concentrations ranged from 86 μM to 378 μM among cell types of CEM, C91-PL, HuT-102, and Jurkat. CEM cells were the most sensitive to EGCG among the cell types tested [7]. In another study, it was found that when HTLV-I-infected T-cell line and healthy control cells were cultured for 3 days in the presence of 27 μg/ml of EGCG, apoptotic DNA fragmentation was significant in HTLV-1 infected cells compared to the healthy control cells [40]. Moreover, EGCG significantly suppressed not only the growth of peripheral blood T lymphocytes of ATL patients, but also suppressed the expression of HTLV-I pX mRNA for more than 90%. There was minimal growth inhibition of the T cells of normal peripheral blood T lymphocytes (PBLs), and the expression of β-actin mRNA was much less suppressed by this treatment with the same concentration of EGCG, indicating that EGCG specifically targets viral proteins [40]. Sonoda and his co-workers investigated the effect of green tea on the diminishment of HTLV-1 provirus in peripheral blood lymphocytes of 83 asymptomatic HTLV-1 carriers [41]. Daily intakes of the capsulated green tea with an estimated EGCG in the plasma to be about 0.3μg/ml for 5 months can significantly diminish the HTLV-1 provirus load as compared with the controls. However, the *in vivo* study on anti-HTLV-1 using green tea as a therapeutic agent is very limited. Besides, the inhibitory effect of EGCG to HTLV-1 lacks high specificity. EGCG also inhibits the proliferation of HTLV-1 non-infected cells, as reported by the Harakeh group [7].

Anti-Herpes simplex virus infection

Herpes simplex virus (HSV) infects skin, mucous membranes and nerves. HSV type 1(HSV-1) infects the mouth, lips, or nose, causing cold sores, and HSV-2 infects the genital and anal area. HSV-2 is highly prevalent worldwide and is a leading cause of genital ulcer disease [42]. In particular, it has been demonstrate that HSV-2 infection greatly increases the likelihood of HIV transmission [43]. Isaacs and co-workers studied the inactivation of HSV-2 virions by green tea catechins. Their experimental data showed that EGCG at 100 μM concentration can completely inactivate (10,000-fold) HSV-2 virions and inactivate HSV-1 virions by 3000-fold. When testing the antiviral ability of EGCG with clinical isolates of HSV-1 and HSV-2, 12.5 μM EGCG exhibited approximately 99% inactivation of HSV-2 clinical isolates. All of the HSV-2 clinical strains were completely inactivated when EGCG of 50 μM was applied. Electron microscopy studies illustrated that the envelopes of HSV particles were damaged in the presence of EGCG [44].

Anti-rotavirus, enterovirus and other virus infection

Rotavirus causes gastroenteritis, especially in children. The extracts from green tea leaves also have been used to examine anti-human rotavirus and enterovirus activities [45]. When cells were treated with the mixture of virus supernatant and diluted EGCG, 50% inhibition of cytopathic effect (CPE) to the infection of five species of human rotaviruses was observed at 8 μg/ml ~ 63.0 μg/ml of EGCG. 100% inhibition of CPE of human rotaviruses could be reached at 125 μg/ml of EGCG [45]. Enterovirus is the most common cause of meningitis and can cause serious diseases, especially in infants. 100% inhibition of enterovirus was observed at 250 μg/ml of EGCG for all enteroviruses examined [45]. EGCG and GCG reduced 95% of the titer of infectious progeny enterovirus71 through suppression of the replication of this virus' genomic RNA according to quantitative real-time PCR analysis [46]. The generation of reactive oxygen species was significantly reduced accordingly with EGCG treatment.

The green tea catechins have been employed to inhibit adenovirus infection in culture cells by Weber and co-workers. Their experimental data demonstrated that addition of 100 μM EGCG to the culture medium of infected cells reduced viral particle production by two orders of magnitude and the virus assembly was greatly reduced at EGCG of 200 μM [47]. Table 1 summarizes the effect of EGCG on a variety of viral infections. The dosages of EGCG vary from the type of cells as well as type of viruses.

Mechanisms of the actions of EGCG interfere with viral infection

Chang and co-workers investigated how the mechanisms of EGCG influence the EBV lytic cycle and revealed that EGCG at 100

μM inhibits EBV lytic replication by inhibiting the expression of viral protein EA-D. EGCG did not inhibit the expression of EBV latent protein EBNA-1, which is a DNA binding nuclear phosphoprotein. But EGCG inhibited the transcription of EBV immediate-early genes and thus resulted in a block of EBV lytic cascade [48].

It is well known that CD4 is a cell surface glycoprotein and is expressed on the surface of T-cells. CD4 acts as a receptor for HIV-1 entry and the binding of HIV-1 envelop protein gp120, with CD4 as the first step of HIV-1 entry into target cells. Kawai group employed a competitive ELISA assay to study the interaction between tea polyphenols and CD4. They demonstrated that EGCG, but not ECG, binds to CD4 and interferes with HIV-1 envelope protein gp120 binding to CD4 [49]. Using nuclear magnetic resonance (NMR) spectroscopy, researchers presented evidence that EGCG binds to CD4 tightly to lead to 100% binding at a concentration of 100 μM. In addition, EGCG binds to the CD4 at the polyphenolic rings of catechin and thus blocks the binding sites of CD4 to gp120, resulting in the inhibition of HIV-1 virus entry [50]. With molecular docking (the "best-fit" orientation of a ligand that binds to a particular protein of interest), molecular dynamics simulation, and binding free-energy calculations, it has been found that binding of EGCG with CD4 can effectively block gp120-CD4 binding because the estimated binding affinity of gp120 with the CD4-EGCG complex is negligible [51]. Gp41 is a glycoprotein and provides assistance in viral-cell fusion during HIV entry into the cell. Gp41 conformational changes have also been reported to be significantly inhibited by EGCG, with EGCG blocking the formation of the fusion-active gp41 six-helix bundles, as measured by ELISA [52].

In an attempt to investigate the possible anti-HIV-1 activity of EGCG and its mechanisms of action in the viral life cycle, Yamaguchi et al. found that: 1) the binding of EGCG to both viral particles and cellular surface was reversible after more than two washes. 2) The inhibitory effect of EGCG on HIV-1 infection is cell-type dependent. For instance, a significant dose-dependent inhibition on HIV-1 viral DNA synthesis was obtained in monocytoid cells THP-1 and human monocyte-derived macrophage cells (MDM), whereas no considerable inhibition on the viral DNA synthesis was noticed in T-lymphoid H9 cells. 3) Investigation on the effect of EGCG on chronically infected THP-1 and H9 cells demonstrated that viral production was dose-dependent inhibited in THP-1 cells, as measured by p24 antigen levels in the culture supernatants. However, no reduction in viral production was observed in chronically infected T-lymphoid cells. 4) EGCG did not inhibit viral mRNA synthesis in all the cell lines tested [53]. Taken together, EGCG exerts inhibition on viral infection via several steps of action in the HIV-1 life cycle.

Table 1: Inhibitory effect of EGCG on a variety of viral infections.

Virus	Dose	Test system	References
HIV-1	0.045 μM	in vitro	[16]
HIV-1	50 μM	Lymphocyte	[18]
Influenza	16 μM	MDCK	[19]
Influenza	28 μM	MDCK	[23]
Influenza	40 mg/kg/day	mice	[25]
HBV	507 μg/ml	HepG2	[32]
HCV	17.9 μM	Huh7.5.1	[33]
HTLV-1	86 μM	C91-PL	[7]
HTLV-1	378 μM	Jurkat	[7]
HTLV-1	350 μM	HuT-102	[7]
HTLV-1	27 μg/ml	PBL, KODV	[40]
HSV-1	100 μM	in vitro	[44]
HSV-2	12.5 μM	in vitro	[44]
HSV-2	50 μM	Vero, CV1	[44]
Rotavirus	125 μg/ml	MA104	[45]
Entervirus	250 μg/ml	MA104	[45]
Adenovirus	200 μM	Hep2	[47]
Adenovirus	714 μM	PCMB	[47]
EBV	100 μM	in vitro	[48]

Mechanisms of EGCG interferes with host cell cycle and *in vivo* studies

In an analysis of ATL-derived HTLV-1-infected cell cycle distribution at which the inhibition was taking place at 300 μM of EGCG, it was found that the cell cycle inhibition occurred at the G_0G_1 phase. The expression of transforming growth factor-α TGF-α), a cytokine with proliferative activities, decreased and the expression level of TGF-β2 (a cytokine with apoptotic and anti-proliferative effects) increased in all the tested cell lines with EGCG treatment. Besides, four important regulators p21 (a cell cycle inhibitor), p53 (the cell cycle regulator), Bax (an inducer of apoptosis), and Bcl-2α (an inhibitor of apoptosis) for cell cycle and apoptosis were examined. The experimental results revealed that p21, p53, and Bax were up-regulated in EGCG-treated cells (Table 2). While the protein expression of an anti-apoptotic member, Bcl-2α was down-regulated in EGCG-treated cells [7]. These experimental data clearly demonstrated the anti-viral apoptotic signaling pathway with EGCG treatment.

There is limited number of reports on the *in vivo* study of EGCG against viral infection. However, it was reported that the daily intake of nine capsules of green tea extract "Nanchariki", which is equivalent to ten cups (120 ml/cup) of green tea for five months, resulted in a significantly diminished human T-cell lymphotropic provirus (HTLV) load in asymptomatic carriers [41]. Using high performance liquid chromatography (HPLC)-UV analysis, it has been determined that nine capsules of the green tea "Nanchariki" contains 246 mg of EGCG. This is no more than one-third of the tolerated dose of green tea in human as reported by Pisters group in a study on maximum-tolerated dose and toxicity of green tea extract to human [54]. With quantitative real-time PCR detection of viral DNA, researchers found that the HTLV-1 provirus load in peripheral blood lymphocytes in the higher provirus load group was diminished after daily intake of the green tea capsules for 5 months [41]. *In vitro* and *in vivo* studies also discovered that it is the carbon of the polyphenol ester bond structure in EGCG and ECG that plays the essential role in the inhibition of proteasome in cancer cells. This proteasome inhibition leads to cell growth arrest in the G_1 phase of the cell cycle, and thus, contributes to the anti-cancer effect of green tea [55].

Table 2: Mechanism of EGCG interference with viral infection.

Virus	Blockage step	References
HIV-1	GP120-CD4 binding	[49-51]
HIV-1	Gp41 fusion	[52]
HBV	transcription	[48]
HCV	Entry	[34-35]
HTLV-1	G_0G_1 phase via p21, p53, Bax, and TGF	[7,55]
EBV	ERK1/2, PI3K/Akt	[25]

Epstein-Barr virus (EBV), also called Human herpesvirus 4 (HHV-4), is one of the most common viruses in humans. It causes infectious mononucleosis, nasopharyngeal carcinoma, and T-cell lymphoma [56-58]. EBV latent infection is strongly implicated in the pathogenesis of several types of cancers, including nasopharyngeal carcinoma (NPC), Hodgkin's disease, and gastric cancer [59]. Very recently, the effect of EGCG on Epstein-Barr virus (EBV) infection and its mechanisms was also investigated. Interestingly, EGCG inhibits gene transcription and protein levels by decreasing the phosphorylation and activation of extracellular signal-regulated kinase 1/2 (ERK1/2) and Akt [25]. It is concluded that EGCG suppresses the activation of MEK/ERK1/2 and PI3K/Akt signaling, leading to the down-regulation of viral gene transcription and protein expression. Table 2 summarizes the mechanism of EGCG interference with viral infection. EGCG can block virus infection at the early stage of viral entry, receptor binding, and promote apoptosis pathway.

PROSPECTS

Studies on green tea extracts used as anti-viral infection demonstrated the power of natural product-inspired drug discovery and development. The significant anti-viral activity of green tea offers promise as adjuncts for anti-viral treatment. In 2006, the FDA approved a special extract of green tea as a prescription drug for the external treatment of genital warts caused by the human papilloma virus (HPV) [60]. One exciting update is that a phase I clinical trial for the evaluation of Safety and Toxicity of EGC in HIV-1-Infected individuals started in December 2010, and is estimated to be completed in July, 2013. In this trial, the safety, toxicity, dose, and antiviral effects of EGCG in capsule form (Polyphenon® E) are determined. Individuals are administered orally twice a day at three different doses in HIV-1-infected with a CD+ T lymphocyte count of at least 250 cells/mm^3. There are two groups of adults in this trial. One is treatment-naïve and the other is treatment-experienced adults who are not on concomitant antiretroviral therapy [61]. Concerns such as the toxicity that EGCG might have on normal cells have been illustrated by a number of groups. EGCG at a concentration of up to 20 μM did not present any damage to rhesus monkey kidney epithelial cells when compared to the control [62]. EGCG is a small molecule with a molecular weight of 458.4. It has been approved as a safe compound by the FDA. However, it should be pointed out that the concentration of EGCG in drinking tea is not sufficient to inhibit disease-related molecules. Thus, up to one gram of green tea solids would be appreciable for anti-disease treatment [54]. EGCG and ECG can be administered orally and are available from the tea plant. It does not cost much for them to be isolated. Besides, as a popular drink, teas are much safer than traditional drugs. Therefore, they offer great advantages over traditional drugs, indicating that EGCG can be a potential therapeutic agent or can act in adjunctive therapy against virus infection.

It should be pointed out that the use of green tea catechins as therapeutic agents has been limited by the catechins' low bioavailability, poor stability under physiological conditions, and intestinal absorption in the body. Hence, like almost all of therapeutic agents, targeted delivery against virus replication is still a major challenge. One approach is to utilize nanotechnology for the targeted delivery of catechins. For example, EGCG can be encapsulated into chitosan-coated nanoliposomes [63]. Chitosan nanoparticles can significantly enhance the intestinal absorption of the green tea catechins due to the stabilization of catechins after encapsulation [64]. To improve bioavailability, surface engineering can also be applied to manufacture tea nanoliposome by a thin film ultrasonic dispersion method [65]. Analogs can be synthesized to improve the stability and bioavailability of EGCG [66].

On the other hand, designing and synthesizing a molecule based on the structure of the natural compound is a major strategy for the development of novel drugs. Song and his co-workers synthesized catechin derivatives with different alkyl chain lengths and aromatic ring substitutions at the 3-hydroxyl group. They investigated the anti-influenza virus activity and cytotoxicity of these EGC derivatives [67]. While modifications of the 5'-hydroxyl group of the trihydroxy benzyl moiety did not notably contribute to antiviral activity, the derivatives carrying chain length (7-9 carbons) showed significant antiviral activity with minimum inhibition concentrations of 5-10 μM in red blood cells. Importantly, the derivatives can inhibit at least five influenza subtypes including human influenza viruses (type A/H1N1, A/H3N2, and B), H2N2, and H9N2 avian influenza virus, showing a potential cross-protection from influenza pandemic [67]. The introduction of long alkyl chains of EGCG by Mori's group enhanced anti-influenza H1N1 virus activity by 24-fold compared to native EGCG [68]. Nevertheless, drug discovery for anti-viral infection is a challenge due to the development of drug resistance by varied viruses. Recent anti-viral researches have shown that a combination strategy may combat viral infection. For instance, an inhibitor of virus infection combining with an anti-inflammatory agent can improve the treatment of viral infection [69]. Taken together, green tea extract EGCG demonstrates its potential as a therapeutic agent. Nevertheless, more studies are necessary for targeted delivery, improved stability, and for the extract to act as an adjuvant for anti-viral treatment.

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