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Editorial Open Access

Potential Applications of Epigallocatechin Gallate-Fatty Acid Derivatives as Antiviral Agents

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Abbreviations

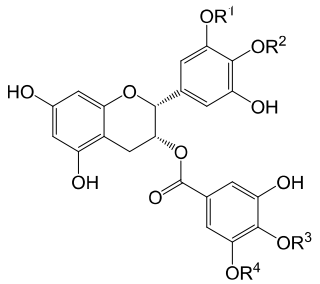
EGCG: (-)-Epigallocatechin-3-*O*-gallate; MDCK: Madin-Darby Canine Kidney; HSV: Herpes Simplex Virus; HPV: Human Papilloma Virus; HBV: Hepatitis B Virus; HCV: Hepatitis C Virus; HIV-1: Human Immunodeficiency Virus-1; EGCG-C_{16}: EGCG-Monopalmitate; EC_{50}: 50% Effective Concentration

Editorial

Epigallocatechin gallate (EGCG) (Figure 1a) is the major catechin component of green tea (*Camellia sinensis*). It has been shown to have antiviral properties against DNA viruses such as herpes simplex virus (HSV; *Herpesviridae*) [1], adenovirus (*Adenoviridae*) [2], human papilloma virus (HPV; *Papovaviridae*) [3], and hepatitis B virus (HBV; *Hepadnaviridae*) [4], and RNA viruses such as influenza virus (*Orthomyxoviridae*) [5], ebola virus (*Firoviridae*) [6], hepatitis C virus (HCV; *Flaviviridae*) [7] and human immunodeficiency virus-1 (HIV-1; *Retroviridae*) [8].

The antiviral mechanisms of the actions of EGCG vary depending on its target virus. According to previous reports, EGCG directly interacts with the lipid membrane and the viral membrane proteins of influenza virus [5] and HCV [7] and interferes with viral entry or membrane fusion steps. ECGC has also been shown to inhibit late infection stages including reverse-transcription [8], transcription [9], integration [8,10], cell signal transduction [11] and protein chaperoning [6]. Although these broad antiviral activities of EGCG are attractive, its poor chemical stability under physiological conditions [12] and low bioavailability (<0.3%) *in vivo* [13] are drawbacks preventing its use in its native form.

There have been several reports in which the chemical, biological and antiviral properties of EGCG were improved by chemical modification. Kouno et al. introduced an *n*-octadecyl group at the 4'-position of EGCG using isocyanate chemistry [14]. They found that EGCG modified with a C_{18} alkyl group possesses increased hydrophobicity and lipid membrane affinity relative to natural EGCG. Mori et al. developed a method to introduce fatty acids into the B-ring or D-ring of EGCG using lipase-catalyzed transesterification [15]. They found that the effectiveness of EGCG-fatty acid monoesters against influenza A/Puerto Rico/8/33 (H1N1) virus was increased in an alkyl chain length-dependent manner in Madin-Darby canine kidney (MDCK) cells [15]. Among EGCG-saturated fatty acid monoesters, EGCG-monopalmitate (EGCG-C_{16}) (Figure 1b) showed the highest anti-influenza virus activity [15]. Although EGCG-C_{16} exhibited a slightly (3.2-fold) higher cytotoxic effect to MDCK cells, it showed significantly (23.5-fold) higher anti-influenza virus activity against the A/Puerto Rico/8/34(H1N1) strain [16]. EGCG-C_{16} inhibited human-, swine- and avian-pathogenic influenza A viruses, and the EC_{50} was between 10 nM and 61 nM, a 7.1-fold to 44-fold lower concentration than unmodified EGCG [16]. A lethal dose of avian-influenza A/H5N2 virus pretreated with EGCG-C_{16} completely prevented the death of embryonated chicken eggs inoculated with the virus by an allantoic cavity route [16].



a) EGCG: R^1=R^2=R^3=R^4=H

b) EGCG-C_{16}: One of R^1,R^2,R^3, or R^4 = $CO(CH_2)_{14}CH_3$, Others=H

Figure 1: Chemical structure of epigallocatechin gallate (EGCG) and its fatty acid derivatives. ***(a)*** A major green tea catechin, epigallocatechin gallate. ***(b)*** EGCG-C_{16} that possesses a palmitoyl group at R^1, R^2, R^3, or R^4.

Oliveira et al. reported that EGCG-C_{16} inhibited the adsorption step of herpes simplex virus infection in Vero cells [17]. Zhao et al. reported that EGCG-C_{16} exhibits significantly higher antiviral activity against porcine reproductive and respiratory syndrome virus than natural EGCG and ribavirin as both pre-treatment and post-treatment [18]. These reports suggest that the pronounced antiviral activities of EGCG-fatty acid derivatives were due to increased permeability through both the viral membrane and the cell membrane.

Although EGCG interferes with different types of viral infections, it is easily oxidized or hydrolyzed under physiological conditions because of the reactive hydroxyl groups in the gallyl moiety in the B-ring and the galloyl moiety in the D-ring [19,20]. However, addition of a palmitoyl group to the B-ring or D-ring prolonged its half-life in a cell culture medium approximately seven-fold [21].

These improved chemical, biological, and antiviral activities of

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this EGCG-fatty acid monoester should expand its application as an antiviral agent and may allow us to combat emerging drug-resistant viruses more effectively.

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