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The Inhibitory Effect of Green Tea Catechins against the COVID-19 Main Protease: Structure-Activity Relationships

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Abstract

COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It became a globally leading public health concern over the past years. However, there are low curative effects and a short supply of specific medicines for the virus treatment. Green tea is a popular beverage all over the word. Catechins are flavan-3-ol compounds that have well concerved structures in green tea. The present work focused on data from in silico and in vitro studies analyzing the inhibitory effect of catechins against the SARS-CoV-2 main protease Mpro and presenting an analysis of the Structure-Activity Relationships. It was shown that gallocatechin gallate (GCG) and epigallocatechin gallate (EGCG) are the most promising catechins for COVID-19 treatment because of the presence of three OH groups on C3′, C4′, and C5′ in the B-ring and the galloyl moiety. The galloyl moiety and OH groups interact with the Mpro active site residues. The findings of the present work showed that the use of alternative drugs from natural herbs, such as green tea, is a promising strategy for preventing the COVID-19 pandemic.

Keywords: Catechins; Green tea; Structure-activity relationships; COVID-19

Abbreviations: C: Catechin EC: Epicatechin; CG: Catechin gallate; ECG: Epicatechin gallate; GC: Gallocatechin; EGC: Epigallocatechin, GCG: Gallocatechin gallate; EGCG: Epigallocatechin gallate; HBV: Hepatitis B virus; DENV: Dengue virus; HCV: Hepatitis C virus; WHO: World Health Organization; HIV: Human immunodeficiency virus; IAV: Influenza

Introduction

Catechins are natural polyphenols which belong to the flavan-3-ols group of flavonoids. They are found in a wide variety of fruits, vegetables and beverages. Camillia sinensis L., commonly known as tea is one of the most popular hot and/or cold drink in the world. Tea consumption has been proved to benefit to human health. Green tea contains eight monomeric catechin compounds that are catechin (C), epicatechin (EC), catechin gallate (CG), epicatechin gallate (ECG), gallocatechin (GC), epigallocatechin (EGC), gallocatechin gallate (GCG) and epigallocatechin gallate (EGCG) [1]. EGCG is the most abundant component, accounting for more than 60% of the total catechin concentrations in green tea, followed by EGC (approximately 20%), ECG (approximately 14%) and EC (approximately 6%) [2]. Catechins are well concerved in the non-fermented green tea. In the fermented products black tea and oolong, the catechins are oxidized during the manufacturing process [3]. Catechin compounds play important therapeutic roles, including antidiabetic [4], antioxidant [5], anti- inflammation [6] and antiviral effects [7]. They are promising antiviral agents against several viruses. In fact, a potent antiviral activity of catechins was proved against several DNA viruses such as hepatitis B virus (HBV) [8] and herpes simplex virus type 1 (HSV-1) [7]. Negative effects of catechins were reported on several (+)-RNA viruses such as dengue virus (DENV) [9] and hepatitis C virus (HCV) [7]. What is more, catechins were identified as a potent agents against (-)-RNA viruses such as human immunodeficiency virus (HIV) [10] and influenza (IAV) [7]. The COVID-19 is caused by

severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It was declared as pandemic by the World Health Organization (WHO) in 2020. As of 30 September 2022, 614.386 M cases of COVID-19, including 6.523 M deaths were reported all over the world [11]. Owing to the low curative effects and the short supply of specific medicines, finding alternative drugs from natural herbs to circumvent COVID-19 can be a promising strategy for preventing the pandemic. In the present work, we presented the inhibitory effects of the green tea catechins on the SARS-CoV-2 main protease Mpro in order to provide a reference for developing anti-COVID-19 agents from the popular beverage green tea. Also, an analysis of the catechins Structure-Activity Relationships was given.

The Potential effect of catechins on SARS-CoV-2 main protease Mpro

Mpro or Nsp5 is an important enzyme for coronaviruses. It is responsible for the proteolysis of coronavirus at the maturation stage. Mpro cleaves 11 sites on the polyproteins pp1a and pp1ab, found in the viral genome. The SARS-CoV-2 main enzyme Mpro allows the formation of several non-structural proteins such as RNA-dependent RNA polymerase, helicase, methyltransferase and endonuclease [12]. Mpro has the catalytic dyad His41-Cys145 on its active site. Thus, SARS-CoV-2 Mpro residues His41 and Cys145 are the most important targets for drugs development. The docking of catechins with the main SARS-CoV-2 protease Mpro showed that they interact with the catalytic residue His41 [13]. Furthermore, EGCG, ECG and EC exhibit stronger interactions with the Mpro active site than the Mpro inhibitor N3 [14]. These three Mpro–flavan-3-ol complexes are highly stable, have low conformational fluctuations and share a similar degree of compactness. Also, EGCG bounds to SARS-CoV-2 Mpro enzyme with higher affinity than the anti-COVID-19 drugs remdesivir and chloroquine [15]. According to Wannes & Tounsi [16], the infusion of tea helped in the treatment of a COVID-19 patient who did not take any medications. In vitro study of Jang et al. [17] showed that EGCG inhibitory activity against SARS-CoV-2 Mpro is dose-dependent. The half inhibitory concentration (IC50) of EGCG was of 7.58 µg/mL without cytotoxicity to HEK 293T cells when the tested concentration was 40 µg/mL [17].

Structure-Activity Relationships of green tea catechins

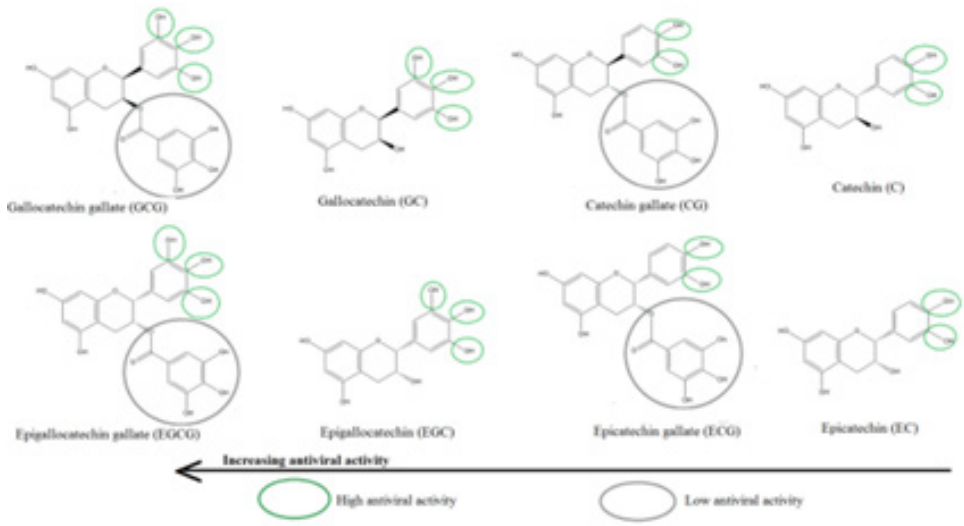

Figure 1: Structure–Activity relationships of the green tea catechins against SARS-CoV-2 Mpro. OH groups and galloyl moiety that result in high/low inhibitory activities respectively are shown in green and grey colors, respectively. [molecules are drawn with ChemDraw 20.0]

In silico study [18] revealed that the compounds C and EC shared the same pharmacophore as the antiviral drug nelfinavir. In polyphenols, the increase in the number of hydroxyl groups lead to the increase of the antiviral effectiveness. The presence of 3′-OH, 4′-OH, and 5′-OH on the B-ring of polyphenols accounts for the antiviral efficiency. In fact, according to the in vitro study of Nguyen et al. [19], the inhibitory effects of catechins against SARS-CoV-2 Mpro were of 53%, 50%, 23%, 21%, 21%, 9% and 8% for respectively EGCG, GCG, EGC, CG, ECG, C and EC, at catechins concentration of 200 mM. EGCG, GCG, and EGC, which contain three OH groups at C3′, C4′, and C5′ in the B-ring, showed higher inhibitory activity against Mpro than EC, C, CG and ECG which contain two OH groups at C4′ and C5′. Therefore, the presence of OH group at C3′ enhanced the inhibitory activity against Mpro.

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In addition, CG and ECG had a higher inhibitory effect against SARS-CoV-2 Mpro than EC and C, and similarly EGCG and GCG had a higher inhibitory effect than GC and EGC. This is due to the presence of galloyl moiety at C3 in the C-ring of CG, ECG, EGCG and GCG. Therefore, the galloyl moiety at C3 of the C-ring increases the inhibitory activity against Mpro. Docking simulations revealed that catechins with galloyl group fit well through hydrogen bonds and other non-covalent interactions into the catalytic amino acid residues (His41 and Cys145) of SARS-CoV-2 Mpro resulting in stabilized complexes [20]. To summarize, catechins with OH group at C3′ have a higher inhibitory effect than catechins with only OH groups at C4′ and C5′ with or without galloyl moiety. Indeed, the inhibitory effect of 3′-OH is higher than that of C3-galloyl moiety [21]. According to the above findings, we propose herein a scheme relating the antiviral activity of the eight green tea catechins to their molecular structure (Figure 1). In this scheme, catechins are classified according to increasing antiviral activity. In Figure 1, the OH groups that have a high inhibitory effect are shown in green and the galloyl moiety that has a low inhibitory effect is shown in grey. The most effective SARS-CoV-2 Mpro inhibitors are GCG and EGCG.

Conclusion

Green tea is a popular beverage all over the world. It contains eight catechins which are catechin (C), epicatechin (EC), catechin gallate (CG), epicatechin gallate (ECG), gallocatechin (GC), epigallocatechin (EGC), gallocatechin gallate (GCG) and epigallocatechin gallate (EGCG). In silico and in vitro studies showed that the catechins are potent anti-SARS-CoV-2. These green tea catechins had a substantial inhibitory effect against the main protease Mpro. From the Structure–Activity Relationships of these catechins, we showed that the hydroxyl groups on C3′, C4′, C5′ in the B-ring and the galloyl moiety contributed to the inhibitory activity of catechins on SARS-CoV-2 Mpro. The effect of 3′-OH is higher than that of C3-galloyl moiety. Thus, GCG and EGCG are shown to be the most promising catechins to treat COVID-19 because they have three OH groups on C3′, C4′, and C5′ in the B-ring and a galloyl moiety that interact with the Mpro active site residues. The findings of the present work showed that the use of alternative drugs from natural herbs, such as green tea, is promising for preventing the COVID-19 pandemic.

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