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Short Communication

Deciphering Interactive Associations of Antiviral and Electron-Shuttling Characteristics of Flavonoid Compounds for Antiviral Drug Development

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Abstract

In face of the 2020 coronavirus COVID-19 pandemic, exploration of feasible medicines and effective medication is of course a top-priority issue to save lives worldwide. This study focused on antiviral properties of flavonoids to decipher synergistic interactions with electron-shuttling characteristics for possible herbal medication in clinical treatment. In fact, the numbers and relative positions of hydroxyl groups all strongly influenced antioxidant activities of flavonoid compounds. In particular, ortho-polyhydroxy benzene-bearing aromatics seemed to trigger antiviral characteristics to be expressed. Prior studies mentioned that ortho and para-polyhydroxy benzene-bearing aromatic structure could exhibit reversible and stable electron-shuttling characteristics. This comparative study suggested the rationale of initiatives for seeking possible methods and strategy of natural medicines with antiviral properties.

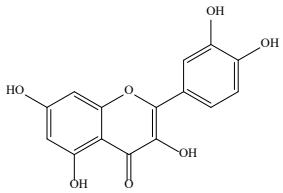
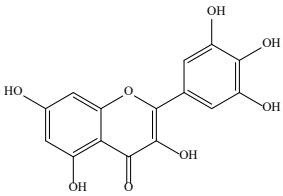
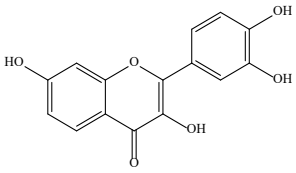
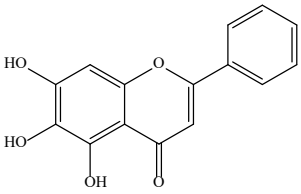
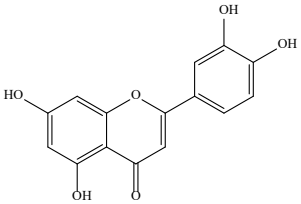
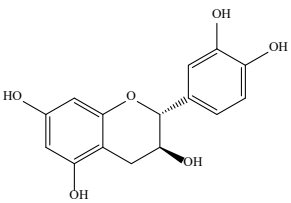
Keywords: COVID-19; Flavonoid; Antivirus; Electron shuttle

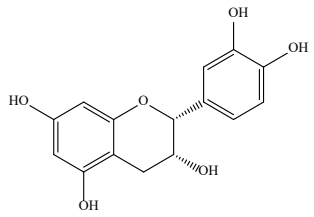
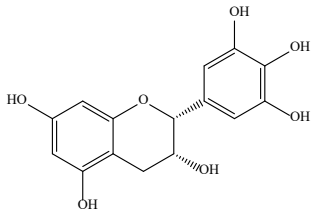
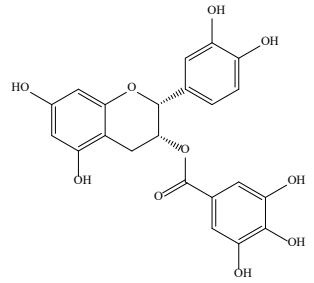
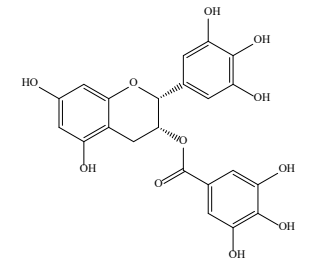
Abbreviations: ADV: Adenovirus; CHIKV: Chikungunya virus; CoV: Coronavirus; DENV: Dengue virus; EV: Enterovirus; ES: Electron shuttle; EC: Epicatechin; EGC: Epigallocatechin; ECG: Epicatechin gallate; EGCG: Epigallocatechin gallate; EBV: Epstein-barr virus; HHV: Human herpesvirus; HIV: Human immunodeficiency virus; IV: Influenza virus; JEV: Japanese Encephalitis virus; MFCs: Microbial fuel cells; NDV: Newcastle Disease Virus; QPD: Qingfei paidu decoction; RSV: Respiratory syncytial virus; VSV: Vesicular stomatitis virus

Introduction

Since the end of 2019, the new coronavirus COVID-19 pandemic took more than half million lives among 21+ million confirmed cases worldwide. As clinical trials recently indicated, remdesivir seemed to be an encouraging coronavirus drug. However, there were still currently not much progress on drug medicines that could effectively inhibit COVID-19. To develop effective medication in such a short period of time to save millions of lives, natural herbs (e.g., Chinese herbal medicine) should first be considered for aspect of not only anti-COVID-19 infection, but also primary health care. As mentioned in literature on natural herbs, flavonoids in polyphenolic compounds (e.g., flavonols-quercetin[1-6], myricetin [2,5,7] fisetin [3,5] and flavones-baicalein[5], luteolin[2][5] [6] and flavanols-catechin[2][4][5][8], epicatechin (EC)[2], epigallocatechin (EGC) [4][6][8], epicatechin gallate (ECG)[4][8], epigallocatechin gallate (EGCG) [4-6][8] would exhibit significant antiviral activities (Table 1). For instance, the flavonoids could effectively inhibit viral protein synthesis and enhance the immune system of host.

Table 1: Comparative list for antiviral characteristics of *ortho* di-hydroxyl group-bearing flavonoid compounds. (CoV(Coronavirus); IV(Influenza virus); DENV(dengue virus); HHV(Human Herpesvirus); ADV(Adenovirus); JEV(Japanese encephalitis virus); RSV(Respiratory syncytial virus); NDV(Newcastle Disease Virus); VSV(Vesicular stomatitis virus); HIV(Human immunodeficiency virus); CHIKV(Chikungunya virus); EBV(Epstein-Barr virus); EV(Enterovirus).

(A) Flavonols	Antiviral
Quercetin槲皮素 	CoV [4,6]; IV [1,2]; DENV [3]; HHV [5]; ADV [5]; JEV [5]; Poliovirus[5]; RSV [5]; NDV [5]; VSV[5]; Hepatitis viruses [5]
Myricetin楊梅黃酮 	CoV [5]; IV [2]; HIV [7]
Fisetin漆黃素 	CoV [5]; EV [5]; DENV [3]; CHIKV [5]
(B) Flavones	**Antiviral**
Baicalein黃芩素 	IV [5]; DENV [5]
Luteolin木犀草素 	CoV [6]; IV [2]; HIV [5]; EBV [5]; EV [5]; JEV [5]
(C) Flavanols	**Antiviral**
Catechin兒茶素 	CoV [4]; IV [2,8]; HIV [5]

Epicatechin 	IV [2,8]
Epigallocatechin (EGC) 	CoV [4,6]; IV [8]
Epicatechin gallate (ECG) 	CoV [4]; IV [8]
Epigallocatechin gallate (EGCG) 	CoV [4,6]; IV [8]; HIV [5]; HHV [5]; Hepatitis viruses [5]

In addition, kaempferol and luteolin could effectively inhibit 3a protein and S2 protein of coronavirus and hemagglutinins of influenza virus [9]. Among flavonoid compounds, quercetin seemed to be more electrochemically favorable to inhibit wide-range viruses (e.g., Adenovirus, Japanese encephalitis virus, Respiratory syncytial virus, Newcastle Disease Virus, Vesicular stomatitis virus, dengue virus, Coronavirus, Influenza virus). As the literature [5] pointed out, quercetin could block the fusion and penetration between the viruses and host cells, and quercetin could exhibit anti-human herpes virus properties. As quercetin could interact with influenza virus hemagglutinin protein, thereby quercetin inhibits fusion of influenza virus and host cells [5]. Furthermore, literature [6] revealed that the flavonoids could effectively inhibit SARS-CoV 3CL protease. protease Literature [10] mentioned that the Chinese herbal medicine- "Qingfei Paidu Decoction" (QPD) might be used to regulate immune system to reduce lung damage. According to composition analysis, the main components were flavonoids (e.g., quercetin, luteolin, kaempferol) [10].

Moreover, the flavonoids could enhance antiviral properties due to interactive synergism. For example, synergies gained from compound prescription of kaempferol and luteolin, or quercetin and antiviral medicine-acyclovir could effectively enhance anti-human herpes virus properties [11]. Thus, this study tended to explore the chemical mechanism about how and why flavonoids could effectively augment antiviral consequence. Considering pathology, oxidative stress induced by viruses [12] could damage the redox balance in the host, and then host immune system would be weakened to favor viral infection to be taken place. Therefore, antioxidant-abundant natural substances may be one of top ranked

candidates to be selected as appropriate medicines to against viruses (e.g., COVID-19). That is, antiviral properties of flavonoids may be strongly associated to antioxidant or redox-rebalancing properties [12].

Regarding redox-associated characteristics of flavonoids, chemical structure-activity relationships should be disclosed. The molecular structure of flavonoid is composed of two benzene rings (A ring, B ring) and one pyran heterocycle (C ring; A ring and C pyran heterocycle fused together) (Figure 1). The higher numbers of hydroxyl groups would own more significant activity of antioxidant. Moreover, the relative positions of hydroxyl groups would significantly affect the antioxidant activity of flavonoids [2,5,13-16]. As literature indicated, the hydroxyl substituents on the B ring would be of great importance for flavonoids to considerably scavenge free radicals. Essentially, the hydroxyl groups on the B ring will transfer protons and electrons to hydroxyl radicals via resonance effect to form relatively stable flavonoid radical during redox reactions.

For the electrochemically steered reactions, ortho and para-polyhydroxy benzene-bearing aromatic compounds could stabilize the free radicals in the electron transfer via resonance effect, thereby promoting the redox reaction [17] (Figure 1). As electrochemical inspection (e.g., cyclic voltammetry assessment and power density analysis upon microbial fuel cells (MFCs) [17-19] indicated, ortho and para-polyhydroxy benzene-bearing aromatic compounds were confirmed to have such redox-mediating (or electron-shuttling) properties, suggesting that ortho-dihydroxy benzene-bearing quercetin was a potential electron shuttle (ES). As proposed in Figure 1 for mechanisms of inter-conversion of quercetin, quercetin was first deprotonated (e.g., chemical (1) in Figure 1), then oxidized to form radical intermediates (e.g., chemical (2) in Figure 1). The following "free radical" electrons would be stably resonant to the carbon bound to be carbonyl group, and the radical electron was transferred to the adjacent carbon attached the strong electron-releasing hydroxyl group to be stabilized (e.g., chemical (3) in Figure 1). Next, deprotonation of this hydroxyl substituent was taken place (e.g., chemical (4) in Figure 1) and was followed to be oxidized for further formation of quinone-type of quercetin. Due to the formation of stable intermediates (Figure 1), the resonant chemical species could be stably and reversibly redox mediating to shuttle electrons between electron donor(s) and acceptor(s). Such mediating characteristics could be considered as keystone properties of redox catalysts to antiviral infection (Figure 1), The effects also reflected significant decreases in internal electron-transfer resistance for stimulating promising power generation in microbial fuel cells (MFCs) [17]-[19]. Thus, the formation of intermediates was more electrochemically favorable to mediate electrons, stimulating The effects also reflected significant decreases in internal electron-transfer resistance for stimulating promising power generation in microbial fuel cells (MFCs) [17]-[19].

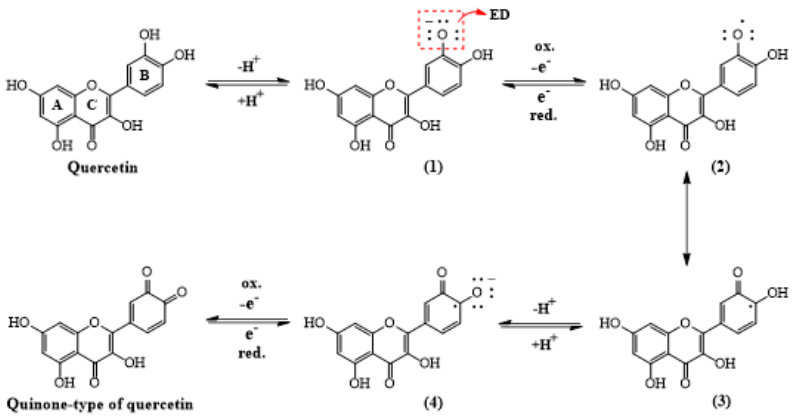


Figure 1: The effects also reflected significant decreases in internal electron-transfer resistance for stimulating promising power generation in microbial fuel cells (MFCs) [17]-[19].

Conclusion

The first-attempt study suggested the associations between antiviral features of flavonoids and electron shuttles (or redox mediators) from the perspective of electrochemistry. Considering chemical structure, flavonoid compounds (e.g., quercetin and catechin) with ortho-dihydroxyl groups on B ring would simultaneously own antioxidant and antiviral properties due to their electron-shuttling activities. As combined synergies gained from compound medicines with flavonoids could enhance physiological activity, this study proposed the flavonoid compounds would also function as electron shuttles (ESs) to catalyze the electron transfer-related reactions in cellular metabolism of humans. That is, follow-up studies should focus on detailed examinations of associations between drug medication and electron mediation.

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Conflict of Interest

The authors declare no potential competing financial interests.

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