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Natural Polyphenols as Inhibitors for the Binding of Covid-19 S-RBD with ACE-2

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Abstract

The binding strength of Covid-19 variants, Omicron BQ.1, XBB.1.5, XBB 1.16, FE.1, EG.5, BA.2.86, HV.1, and JN.1, with the ACE-2, was calculated *in silico* and evaluated with previous variants; the binding strength of new variants is XBB.1.5 << BA.2.86 < Delta < JN.1 < HV.1 < BA.1 << BA.2. The binding strength of Omicron JN.1 was similar to that of Delta, and that of others was less than that of BA.2.86. The binding inhibition of natural polyphenols was analyzed using a popular Omicron JN.1. The natural polyphenols were (-) Catechin, (+) Catechin, (+) epicatechin, apigenin, apigetrin, daidzein, quercetin, genistein, and oleuropein. The ionization of phenolic hydroxy groups was defined based on the atomic partial charge of oxygen. Polyphenols' ionized hydroxy groups inhibited the binding of JN.1 S-RPB with ACE-2.

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Introduction

The mutation of COVID-19 is too fast, following the analysis of transmissibility and estimation of the multiplication are delayed. Preventing infection is an urgent subject. The previous analyses [1] suggested that the inhibitor candidates are citric acid and related Creb's cycle organic acids, synthesized from glucose as normal metabolic processes. Kids constantly produce these acids and then synthesize related amino acids and other important compounds for growing. Aging reduces such activity; therefore, adults must eat food containing essential metabolites. This known metabolism may support the idea that kids are less infected [2]. Children's self- protection against COVID-19 was reported, even though children do not have a particular compound, and the fundamental defense mechanisms should be the same as those of adults [3,4]. It may be the activity of ordinal metabolisms and mass production of various compounds for their growth. Aged people may not have enough vital metabolisms to protect from COVID-19 infection if they do not eat balanced foods. Food habits may affect the mortality of meat-eating and vegetable-eating populations by comparison to their food habits. Before vaccination became a common practice, the USA's total death/ and infectibility/population ratio was approximately 14 and 10 times Japan's total death/ and infectibility/population ratio. America's relative intake of citric acid-related metabolites [5] is lower than Japanese. The "Healthy Eating" report presented the regional food habits [6], suggesting transmissibility and mortality are very high in certain countries. Excess dairy and animal protein eating seems to relate to the urgent problem. We have to analyze the evidence continuously based

on quantitative analytical chemistry.

Myocarditis and/or pericarditis were observed after SARS-CoV-2 mRNA vaccination with a predilection for adolescent and young adult males [7]. We need temporary help with vaccines; however, we must maintain our daily health by exercising and eating balanced food. We should avoid continuous vaccination to maintain our immune system as our normal condition against unpredictable viruses and bacteria. Continuous vaccination is like living in a greenhouse and eating supplements. People who used to live in such conditions are vulnerable outside of the greenhouse. The unbalanced habits seem to be clear evidence for COVID-19 transmissibility and mortality like diabetes. Understanding fundamental chemistry should help individuals reconsider their lifestyle, including vaccination and drugs; therefore, the contribution of natural polyphenols as binding inhibitors was investigated.

Experimental

The experimental method was the same as that performed previously [1]. Preparation of mutants was performed using the same method used for quantitative analysis of enzyme reactivity, such as alanine racemase, serine racemase, alcohol dehydrogenase, cinnamyl alcohol dehydrogenase, D-amino acid oxidase (DAO), and D- aspartic acid oxidase (DDO) [1a]. Replaced amino acid of wild-type S-RBD and optimized the new variant structures. Then, the binding inhibitor candidates were located above the JN.1 S-RBD, and the structures were optimized. The complexes of JN.1 S-RPD with inhibitor candidates faced the extracted ACE-2, and their conformations were optimized to obtain the inhibitor candidate performance. The MI energy values were obtained from their original and the complex's values using the following equation: MIFS = {fs (S-RBD) + fs (ACE-2)} - FS (S-RBD and ACE-2 complex), where fs is the final structure energy value of individual molecule, fs and FS are the final structure energy value of the initial and the complex. The experimental processes are shown in Figure1. Computational chemical calculations were performed using a DCPIx86-based PC with an Intel Core™i7-2600 cpu 3.40 GHz (Dospara, Yokohama) with the CAChe program (Fujitsu, Tokyo). The minimum energy level was 10^{-7} kcal mol^{-1}.

Results and discussion

Green and black tea components inhibited the binding of S-RBD with ACE-2 [8-12]. The components Epigallocatechin gallate (EGCG), Theaflavin digallate (TFDG), and Catechin are polyphenols. Phenolic compounds are classified as acidic compounds, but the dissociation constant of common phenolic compounds is more than 9; therefore, common phenolic compounds are neutral in physiological conditions. Generally, ionized acidic compounds inhibit the binding of S-RBD with ACE-2, and basic amino acids enhance the binding strength [13]. The molecular form of phenolic compounds did not inhibit the binding and just adsorbed on the binding site. The dissociation constant (p*K*a) of EGCG, TFDG, and Catechin was not known. Therefore, the dissociation of these compounds was estimated from the atomic partial charge (apc) of their phenolic hydroxy groups. A p*K*a prediction method for acidic compounds used the apc value of the hydroxy group of oxygen and hydrogen calculated using the MOPAC AM1 program [14]. While the hydrogen partial atomic charge value exceeded 0.23 au (MOPAC AM1), the p*K*a value was less than 7.5. The method was applied to estimate the dissociation of green and black tea components.

The calculated apc value of several hydroxy group hydrogen of these three compounds was more than 0.23 au [13], and these gallate hydroxy groups indicated the possible ionization because of their

hydrogen apc values. Tea leaves' partly ionized polyphenols were applied to binding inhibition analysis. First, the ionized compounds were docked at the BA.2.86 S-RBD docking site; then, the complex faced the ACE-2 docking site and optimized the structures. The partly ionized polyphenolic compound (TFDG) inhibited the binding of BA.2.86 S-RBD with ACE-2. This *in silico* analysis supported the idea that these phenolic compounds in tea indeed inhibit the binding of S-RBD with ACE-2.

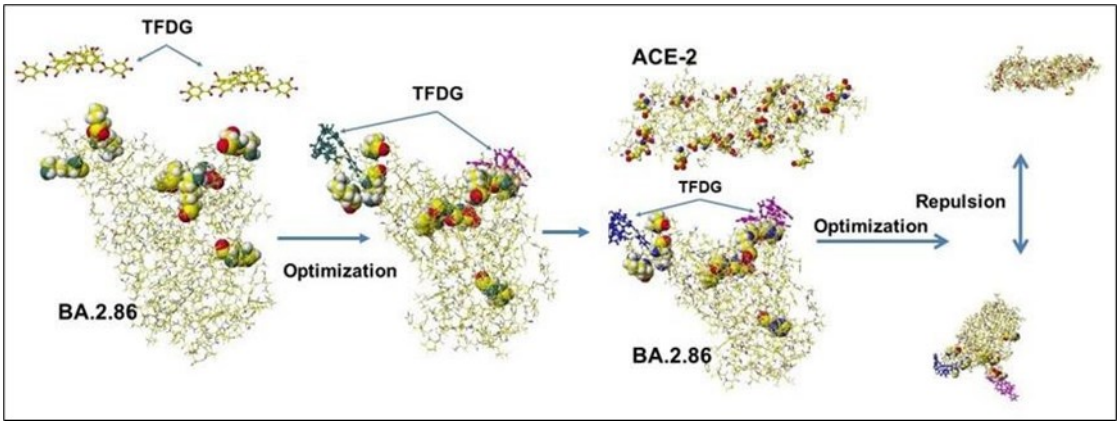

Figure 1. Structure of tea component's polyphenol TFDG and the in silico analytical processes for the binding inhibition analysis

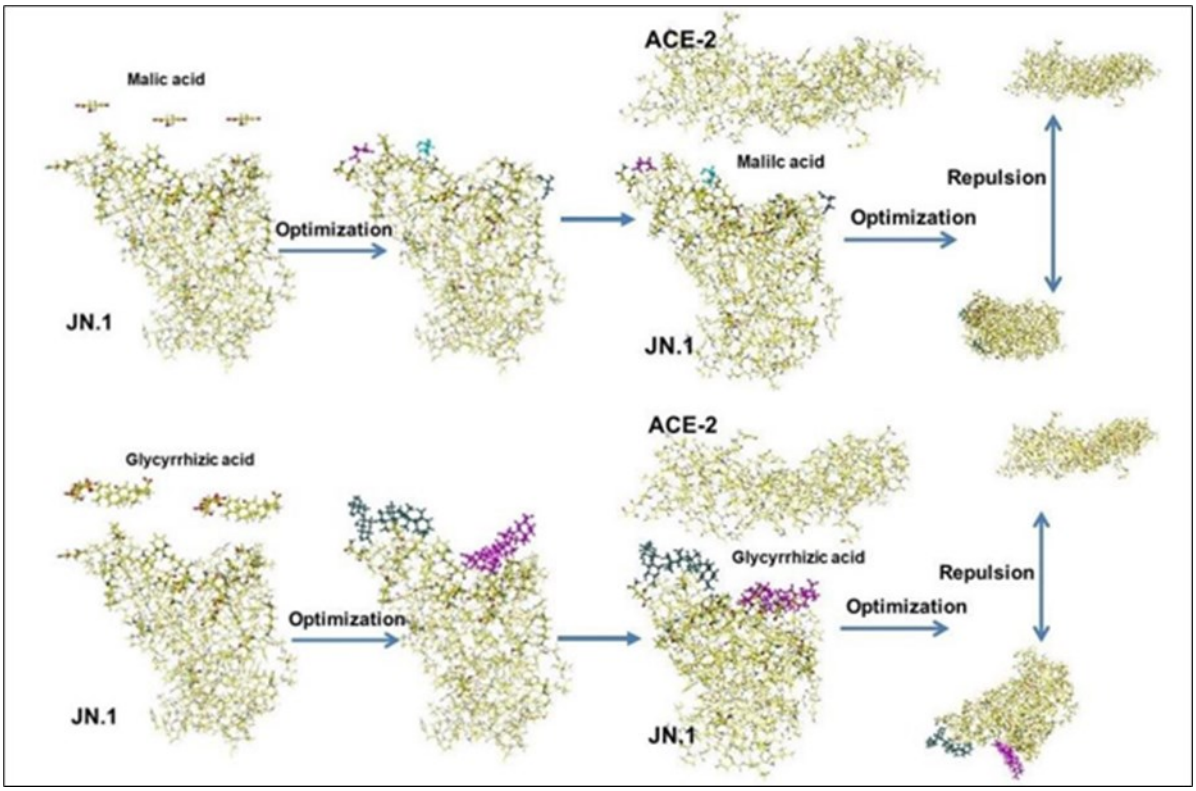

Figure 2. Inhibition of malic acid and glycyrrhizic acid of Omicron JN.1 binding with ACE-2, these binding inhibitors are indicated as color molecules for easy identification of their binding location with S-RPD

A popular Omicron JN.1 is further mutated valiant from Omicron XBB.1.5 and exhibited stronger binding affinity with ACE-2 than that of BA.2.86. The mutation L455S increases the flexibility of JN.1 R454. The mutation contributed strong binding affinity of JN.1. The binding strength (molecular interaction energy kcal mol- 1) of new variants is XBB1.5 (373.9 kcal mol-1) << BA.2.86 (556.2 kcal

mol-1) < Delta (594.2 kcal mol-1) < **JN.1** (632.3 kcal mol-1) < HV.1 (702.7 kcal mol-1) < BA.1 (761.7 kcal mol-1) << BA.2 (904.3 kcal mol-1) based on protein (S-RBD) and protein (ACE-2) interaction energy values, calculated using *in silico* analysis [15]. Malic acid and glycyrrhizic acid inhibited the binding with ACE-2. Furthermore, polyphenols on glucose-induced metabolic changes in healthy human subjects may inhibit the binding; therefore, several polyphenols were subjected to whether they inhibit the binding or not. The malic and glycyrrhizic acid inhibition of the binding of JN.1 S-RBD and ACE-2 are shown in Figure 2. These compounds inhibited the binding of JN.1 with ACE-2.

Polyphenols have been used for the oral glucose tolerance test as a way to diagnose diabetes [16]. Tea leaf components (polyphenols) inhibit the binding of COVID-S-RPD with ACE-2. Therefore, the feasibility of several polyphenols, such as flavanols, isoflavones, and flavonols being contained in natural plants [16] has been analyzed their feasibility as the binding inhibitors of S-RBD with ACE-2. The structures of used polyphenols are shown in Figure 3. The process was the same as that performed for tea TFDG (Figure 1). Some molecular sizes were large and repulsed each other; therefore, only two molecules were used as the inhibitors. While the phenolic hydroxy group is the molecular form, the phenolic compounds bind to ACE-2 via hydrogen bond, and the ionized hydroxy group is repulsed from acidic amino acids via ion-ion repulsion.

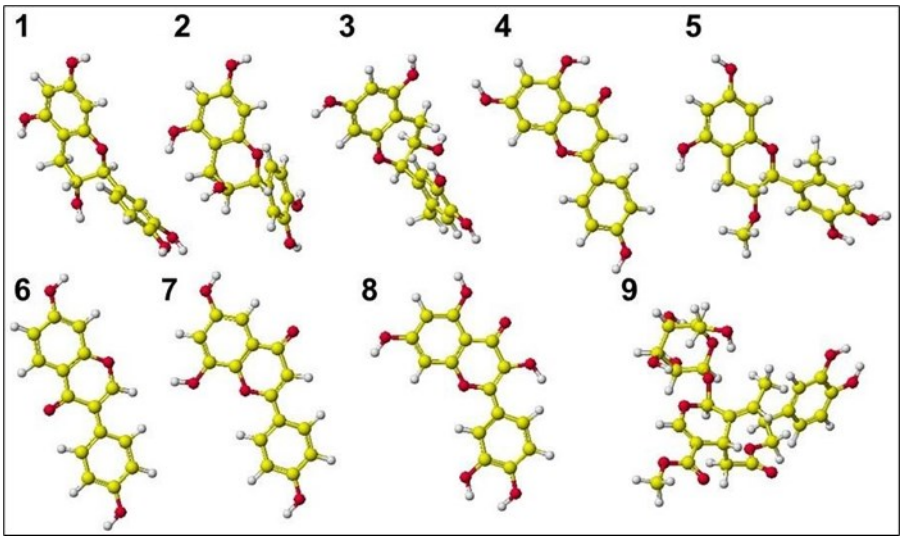

Figure 3. Chemical structure of polyphenols, 1: (-) Catechin, 2: (+) Catechin, 3: (-) Epicatechin, 4: Apigenin, 5: Apigetrin, 6: Daidzein, 7: Genistein, 8: Quercetin, 9: Oleuropein; Red (black), yellow (gray), and white balls are oxygen, carbon, and hydrogen.

The optimized complexes of Omicron JN.1 with these polyphenols faced the ACE-2 binding site, and the conformed structures were optimized. The pre and post-optimization structures are shown in the following Figure 4, which exhibit the reaction process of (-) Catechin, (+) Catechin, (+) epicatechin, apigenin, apigetrin, daidzein, quercetin, genistein, and oleuropein.

For the inhibitor search study, three inhibitor candidates were located above S-RBD; however, the necessary number of inhibitors was varied due to the molecular size and the repulsion between the inhibitor candidates. One Genistein, two (-) Catechin, (-) Epicatchin, and Quercetin were enough to inhibit the binding with ACE-2. Natural food components can protect against infection by COVID-19 in computational chemical analysis; however, the actual steric hindrance, the quantitative analysis of biological reactions, is still difficult. These phenolic compounds inhibited the binding of JN.1 S-RBD

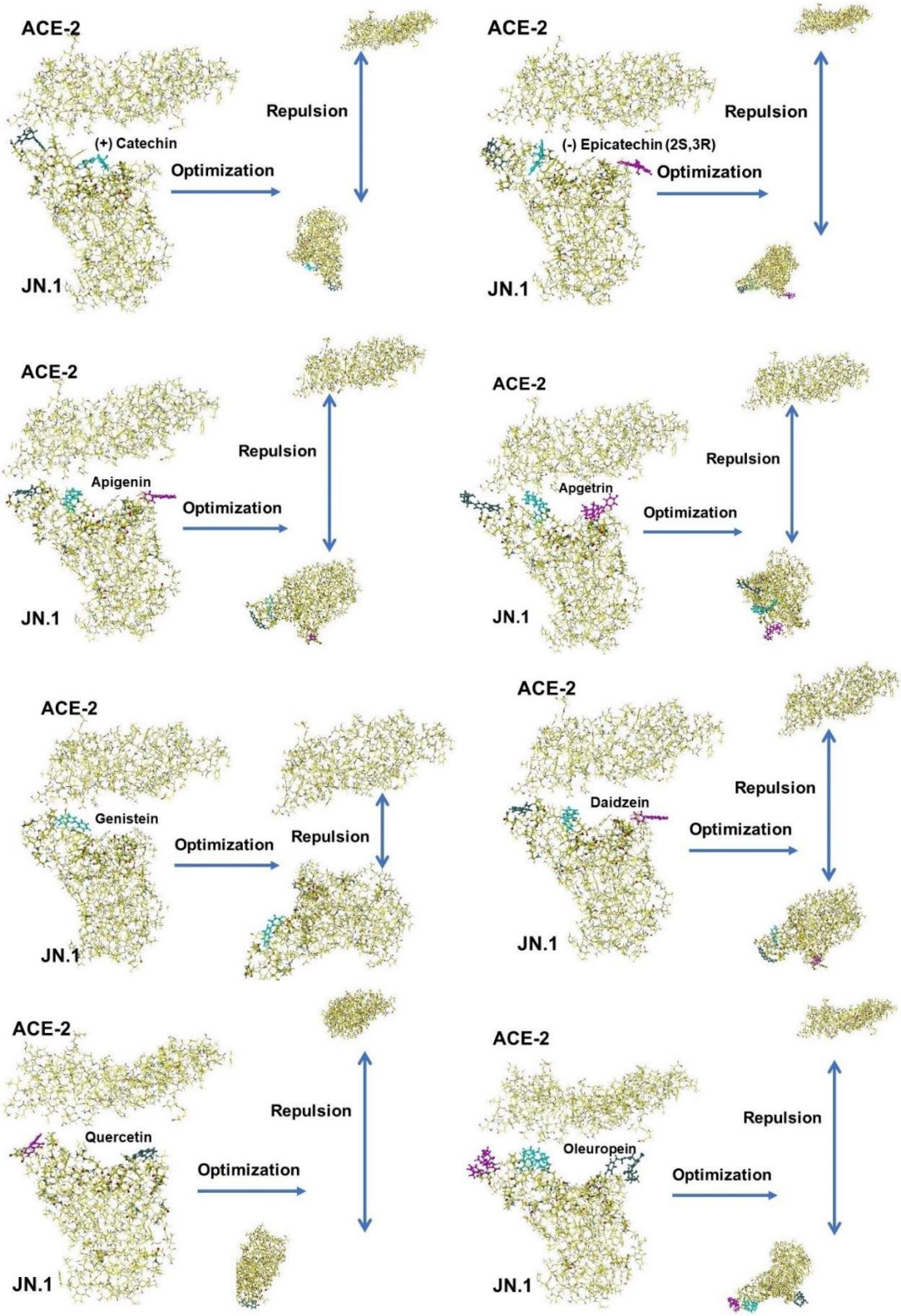

Figure 4. Optimization of ACE-2 and JN.1 and a polyphenol complex, Color molecules are polyphenols.

with ACE-2.

Natural immunity is considered superior to vaccine-induced immunity. A growing body of literature provides evidence on natural immunity after COVID-19 infection that not only confers robust, durable, and high-level protection against COVID-19 [17]. Herbal medicine is exploring untapped therapeutic potential in neurodegenerative disease management [18], and various effective compounds have been identified in herbal medicines [19]. The *in silico* analysis of the binding inhibition by natural polyphenols supported the effect of food components that may inhibit the infection and help natural immunity. Several RNA vaccines are developing. mRNA vaccines produce new, toxic proteins to viruses and bacteria; however, the products are new intruders to our immune system that may cause some side effects. While we are healthy, our bodies can compete against intruders. However, aging and other incidents weaken our metabolic system, and our immune system is also weakened. Why not produce mRNA to recover our weakened metabolism? The best approach, now we can do, is to reconsider our eating habitude and do certain exercises. One example against COVID-19 infection is eating certain foods containing compounds that inhibit the S-RBD binding to ACE-2.

Conclusion

In physiological conditions, natural compounds with ionized acidic groups (carboxy and phenolic hydroxy) may inhibit the binding of S-RBD with ACE-2. The *in silico* analysis quantitatively demonstrated that the natural polyphenols inhibited the binding of JN.1 S-RBD with ACE-2. Therefore, balanced food habitude can protect against COVID-19 infection. Remain question is how to inhibit virus multiplication. The possible compounds are oligosaccharides that bind glycoproteins and reduce their activity. The oligosaccharide effect may support pros ivermectin. Various oligosaccharides and polyphenolic compounds are contained in natural foods. Therefore, eating colorful vegetables may protect us.

Conflict of interest

This work was done in personal interest without any funds.

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