



## The potential of polyphenols from natural ingredients against SARS-CoV-2 infection: A review

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### ABSTRACT

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All countries in the world are facing the coronavirus disease-19 (COVID-19) pandemic which has resulted in various crises. To date, there is no effective treatment in controlling COVID-19. Many clinical trials of approved drugs against COVID-19 were conducted. However, the results were inconclusive, even severe adverse effects were reported. The new effective drugs are therefore urgently needed. Herbal medicines have been widely used by community to enhance the body immune system during COVID-19 pandemic. Polyphenols are large group of active compounds found in the natural ingredients. These compounds have been proven to have biological activity against various pathogen infections including viral infection. During COVID-19 pandemic, various polyphenol compounds from various medicinal plants have been investigated for their activity against severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) both *in silico* and *in vitro*. Among the polyphenols investigated, some of them namely papyriflavonol, catechin gallate, galocatechin gallate, luteolin, quercetin, tangeretin, naringenin, herbacetin, emodin, eriodyctiol, fenoterol, baicalin, myricetin, quercetagetin exhibited strong activity against SARS-CoV-2. The possibilities of mechanism of actions as antiSARS-CoV-2 of these polyphenols were 1) bind to the N protein causing the inhibition of viral transcription and replication; 2) inhibit the binding of S protein to ACE2 receptors preventing the entry of the virus into the host cells; 3) inhibit 3CL<sup>pro</sup> function inhibiting the viral transcription and maturation; and 4) bind directly to the ACE2 receptor. In conclusion, some polyphenol compounds from nature ingredients are potential to develop to be future antiSARS-CoV-2. However, further the pre-clinical and clinical studies are required to strengthen existing evidence.

### ABSTRAK

Seluruh negara di dunia sedang menghadapi pandemi COVID-19 yang telah mengakibatkan krisis di berbagai negara di dunia. Sampai saat ini belum ada pengobatan yang efektif dalam mengendalikan COVID-19. Banyak uji klinik terhadap obat yang ada dilakukan untuk melawan COVID-19. Namun hasilnya belum dapat disimpulkan dengan baik, bahkan timbulnya efek samping yang cukup serius telah dilaporkan. Ketersediaan obat baru yang efektif dengan demikian sangat diperlukan. Tanaman obat telah digunakan secara luas oleh masyarakat untuk meningkatkan sistem imun tubuh selama pandemic COVID-19. Polifenol adalah kelompok senyawa yang banyak ditemukan dalam tanaman tersebut. Senyawa ini telah dibuktikan mempunyai aktivitas biologi melawan berbagai infeksi patogen termasuk infeksi virus. Selama pandemic, berbagai senyawa polifenol dari berbagai tanaman obat telah dikaji aktivitasnya melawan SARS-CoV-2 baik secara *in silico* dan *in vitro*. Di antara senyawa polifenol yang dikaji, beberapa senyawa yaitu papiriflavonol, katekin galat, galokatekin galat, luteolin, kuersetin, tangeretin, naringenin, herbacetin, emodin, eriodiktiol, fenoterol, baicalin, myricetin, dan kuercetagetin menunjukkan aktivitas yang kuat melawan SARS-CoV-2. Kemungkinan mekanisme aksi sebagai antiSARS-CoV-2 dari senyawa polifenol tersebut adalah 1) berikatan dengan protein N yang menyebabkan hambatan transkripsi dan replikasi virus; 2) menghambat ikatan protein S dengan reseptor ACE2 yang mencegah masuknya virus ke dalam sel inang; 3) menghambat fungsi 3CL<sup>pro</sup> yang menghambat replikasi dan pematangan virus; 4) berikatan langsung dengan reseptor ACE2. Simpulan, beberapa senyawa polifenol dari bahan alam potensial untuk dikembangkan sebagai antiSARS-CoV-2 di masa depan. Namun demikian, penelitian pre-klinik dan klinik selanjutnya sangat diperlukan untuk memperkuat bukti yang ada.

## INTRODUCTION

All countries in the world are facing the coronavirus disease-19 (COVID-19) pandemic which has resulted in crises in various sectors. Ten of millions of people have been infected worldwide and millions of them have died from this disease. Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is a coronavirus that causes COVID-19 which has a major impact on human health globally.

To date, there is no specific pharmacological treatment that has been recognized as effective in decreasing viral load and reducing the spread of the virus to control COVID-19. In several countries, studies have been conducted using patients who test positive for SARS-CoV-2 and received drugs therapy such as chloroquine, hydroxychloroquine, azithromycin, lopinavir-ritonavir, favipiravir, remdesivir, ribavirin, interferon, convalescent plasma, steroids, and anti-IL-6 inhibitors. However, a number of side effects such as QT prolongation, torsade de pointes, hepatitis, acute pancreatitis, neutropenia, and anaphylaxis have been reported, especially in patients treated with chloroquine, hydroxychloroquine, azithromycin, and lopinavir-ritonavir.<sup>1</sup>

Currently, it is necessary to find a more effective and safe strategy to deal with this pandemic. Further studies are needed to determine whether alternative medicine with compounds from natural ingredients such as polyphenolic compounds offers a solution in controlling COVID-19. The purpose of this article is to evaluate the existing literature regarding the potential of polyphenols from natural ingredients to fight SARS-CoV-2 infection as the cause of the COVID-19 pandemic.

## DISCUSSION

### Polyphenol compounds

Polyphenols are the largest group of bioactive compounds containing plants. They are produced as secondary metabolites with protective functions against ultraviolet radiation, pathogen aggression, and protection against oxidative stress. Structurally the term polyphenol refers to the presence of one or more phenolic rings with a hydroxyl group. Polyphenols can be classified into flavonoids such as anthocyanins, flavones, flavanones, flavonols, isoflavones, and flavan-3-ols, phenolic acids, polyphenolic amides, and other polyphenolic compounds such as stilbenes or ellagic acid (FIGURE 1).<sup>2</sup>

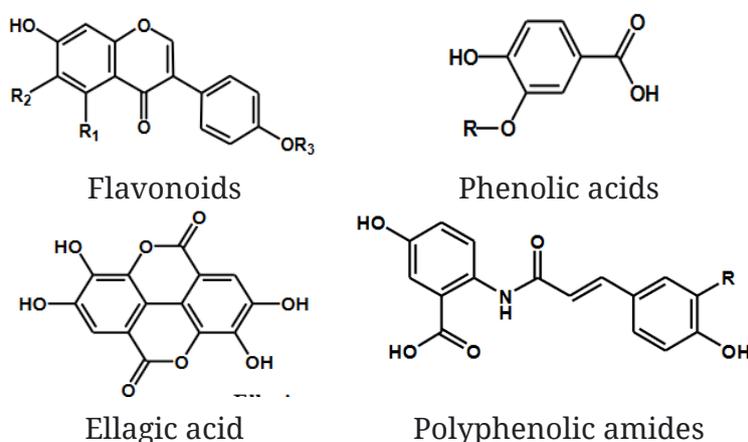


FIGURE 1. Chemical structures of polyphenols class

Polyphenols have been widely studied and are known to provide many benefits for human health, such as polyphenols having antioxidant, anti-inflammatory, immunomodulatory, antitumor, prebiotic and other health benefits. Polyphenols show benefits for the prevention and treatment of various diseases. The beneficial pharmacological properties of polyphenols also exhibit inhibitory activity against viral components and action.<sup>3</sup>

### Polyphenols and virus infection

Polyphenols are widely known for their antioxidant and anti-inflammatory activities. Many studies showed this bioactive compound has antiviral potential. Many studies have investigated the effect of polyphenols against various viral infections by interfering with the viral life cycle and stopping viral replication, enhancing the immune response, and protecting against inflammation in infected patients. The use of polyphenols has been widely used in viral infections such as HIV, hepatitis B virus, hepatitis C virus, and influenza

virus. Other studies have shown the effectiveness of polyphenols against several viral pathogens, such as Epstein-Barr virus, enterovirus 71, herpes simplex virus (HSV) and other viruses that cause respiratory tract-related infections.<sup>1,4</sup>

Polyphenol compounds have broad-spectrum antiviral properties that are potentially useful in various enveloped viruses. Polyphenols have a-glucosidase inhibitory activity on viral envelope glycoproteins. Polyphenols also prevent the enzymatic activity of viruses by inhibiting the multiplication and function of viral glycoproteins which are the main components of nucleocapsid formation in viruses.<sup>5</sup>

The polyphenolic compound resveratrol (FIGURE 2), is known to have antiviral activity. The mechanisms especially are its ability to inhibit viral replication through several mechanisms, namely through inhibition of the initial expression of viral proteins (ICP-4 and-27), through inhibition of the NF- $\kappa$ B signaling pathway, and through activation of AMPK/Sirt1 in host cells.<sup>4</sup>

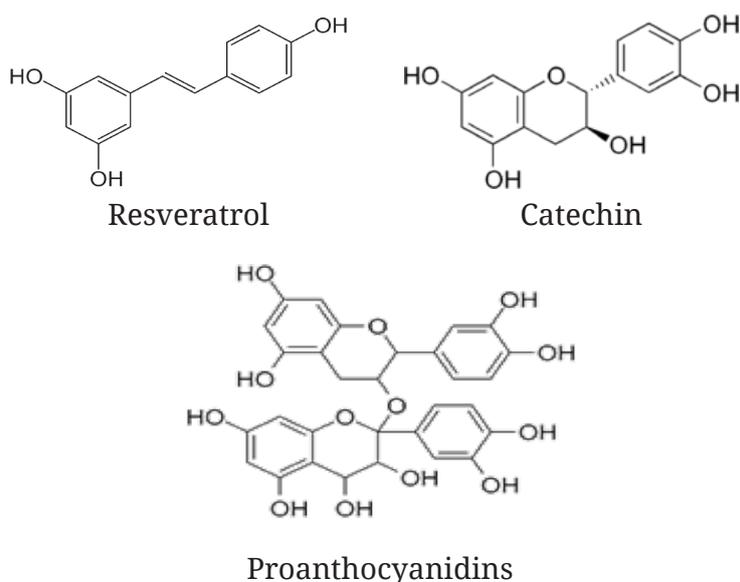


FIGURE 2. Some potential polyphenols as antiviral

Grape pomace extract (GPE) has been reported as an excellent source of bioactive compounds especially polyphenols, resveratrol, catechins, and proanthocyanidins (FIGURE 2). Evidence suggests antiviral activity of GPE against various viral pathogens, such as HIV type 1, human enterovirus, Feline calicivirus (FCV) F9, murine norovirus (MNV-19), hepatitis A virus, and hepatitis C virus. A variety of different mechanisms of action have been demonstrated in such studies such as downregulation of HIV-1 entry coreceptor expression, suppression of viral replication through reduced COX<sub>2</sub> expression and regulation of NF-κB and MAPK signaling pathways and reduction of viral inflammation for anti-HCV activity.<sup>1</sup>

An *in vitro* study reported the effect of GPE against respiratory syncytial virus, using the airway epithelial cell model A549. It was shown that GPE interferes with the expression of nucleoproteins and fusion proteins thereby reducing viral replication. In addition to direct antiviral activity, GPE was reported to be effective in reducing the pathological complications of viral infections at the respiratory level, reducing mucin expression whose levels are elevated during airway mucosal inflammation and decreasing pro-inflammatory interleukins, including IL-1β, IL-6, and IL-8.<sup>6,7</sup>

Polyphenolic compounds are currently being tested against coronavirus activity. Many studies around the world are trying to find and develop specific antivirals to prevent and control coronavirus infections. So that polyphenol compounds are promising for use in coronavirus infections including SARS-CoV and MERS-CoV.<sup>3</sup>

### Potential of polyphenols against SARS-CoV-2

A study was carried out to elucidate the specific target of polyphenols in anti-coronavirus activity. The anti-MERS-CoV and SARS-CoV activities were

tested from ten different polyphenols isolated from the *Brussonetia papyrifera* plant. All isolated compounds tested at concentrations ranging from 0 M to 200 M showed dose-dependent inhibitory activity against the MERS-CoV and SARS-CoV protease and found a inhibitory concentration 50% (IC<sub>50</sub>) at concentrations ranging from 3.7 to 66.2 μM.<sup>8</sup> Among the polyphenols tested, papyriflavonol is the most active with an IC<sub>50</sub> value of 3.7 μM (FIGURE 3).

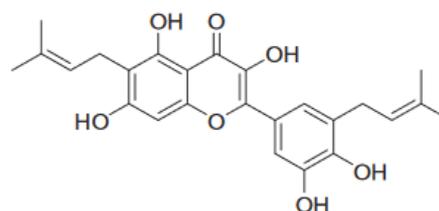


FIGURE 3. Papyriflavonol isolated from *B. papyrifera*.

Other studies have shown that several polyphenolic compounds have been tested for screening SARS-CoV nucleocapsid protein inhibitors. The polyphenolic compounds studied, namely catechin gallate and gallic acid gallate (FIGURE 4), showed anti-SARS-CoV activity on nucleocapsid proteins. This study demonstrated the ability to attenuate the protein binding activity of the SARS-CoV nucleocapsid at a concentration of 0.005 μg/mL, at 0.05 μg/mL the compound gave an inhibitory activity of more than 40%, and at the same concentration IC<sub>50</sub> was found. These results seem to clarify the mechanism of action and targets of the antiviral activity of polyphenols against SARS-CoV.<sup>1</sup>

The polyphenolic compounds luteolin and quercetin (FIGURE 5) were reported to be able to inhibit SARS-CoV infection by preventing the entry of the virus into Vero E6 cells with EC<sub>50</sub> values of 10 mM and 83 mM, respectively. Luteolin was found to bind with high affinity to the SARS-CoV S protein, thus suggesting an antiviral mechanism that causes disruption of viral S protein function.<sup>9</sup>

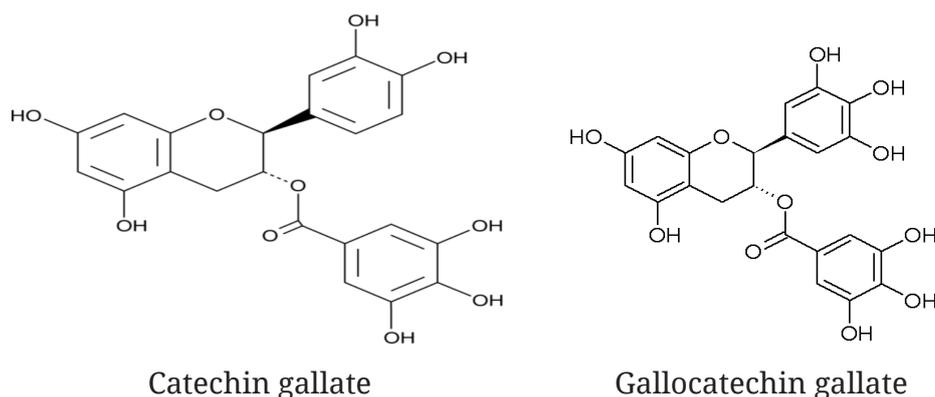


FIGURE 4. Catechin gallate and gallocatechin gallate as potential anti COVID-19.

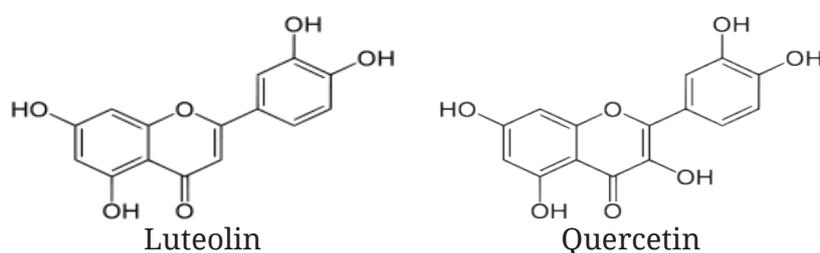


FIGURE 5. Luteolin and quercetin as potential anti COVID-19.

3-Chymotrypsin-like protease (3CL<sup>pro</sup>) is a nonstructural protein of the coronavirus, which has been identified as the most attractive target for combating SARS-CoV. Its function is in the cleavage of polyproteins into viral replication-associated proteins, which is an important process for SARS-CoV replication and maturation. SARS-CoV-2 also has 3CL<sup>pro</sup> with a sequence identity of 96.1% compared to SARS-CoV and MERS-CoV. Another important function of 3CL<sup>pro</sup> is the cleavage of host proteins associated with the innate immune response, including the potent signal transducer and transcription activator 2 and the transcription factor NF- $\kappa$ B as a modulating signaling protein.<sup>10</sup>

The SARS-CoV-2 polyprotein is processed by the main protease 3CL<sup>pro</sup> (also known as M<sup>pro</sup>) and by the papain-like protease (PL<sup>pro</sup>). These proteases are involved in the replication and transcription of SARS-CoV-2 especially 3CL<sup>pro</sup> which plays an important role in polyprotein processing and viral maturation. Therefore, 3CL<sup>pro</sup> is one of the targets of SARS-CoV-2 drugs, and

studies have shown that the development of antiviral agents targeting 3CL<sup>pro</sup> can provide an effective treatment against coronavirus infections.<sup>11</sup>

By neutralizing 3CL<sup>pro</sup> can prevent viral maturation and restore the natural immune response associated with SARS-CoV-2 infection. A series of inhibitors have been reported to play a role against 3CL<sup>pro</sup> from coronavirus to prevent viral replication.<sup>12</sup>

The water-soluble flavonoid quercetin shows activity that can inhibit various viruses. Its main mechanism of action is via suppression of 3CL<sup>pro</sup>. Molecular docking studies and enzymatic inhibition assays clearly demonstrated the binding and inhibition of 3CL<sup>pro</sup> by quercetin-3- $\beta$ -galactoside. Based on the similarities between the structure and physical function of 3CL<sup>pro</sup>, it can be concluded that quercetin can bind to 3CL<sup>pro</sup> of SARS-CoV-2 and inhibit its catalytic activity similar to its effect on various other viruses.<sup>3</sup>

Quercetin as a natural compound has low cellular toxicity activity and

was found to accumulate in various tissues, including the lungs, which would facilitate interaction with SARS-CoV-2. Quercetin not only exhibits viral replication inhibitory activity with interactions occurring at the 3CL<sup>pro</sup> active site, but may also be able to fight comorbidities in elderly patients.<sup>13</sup> Research by Ghosh *et al.*<sup>15</sup> showed inhibition of 3CL<sup>pro</sup> was demonstrated *in silico* and *in vitro* with the polyphenols

epigallocatechin gallate (IC<sub>50</sub> = 73 mM), gallicocatechin gallate (IC<sub>50</sub>=47mM) and quercetin (IC<sub>50</sub>=73mM).<sup>14</sup> Other citrus flavonoids such as tangeretin and naringenin (FIGURE 6) and polyphenols from *Curcuma* spp. also reported to bind strongly to the 3CL<sup>pro</sup> binding domain of SARS-CoV2 when interacting with protein S and angiotensin-converting enzyme-2 (ACE2) *in silico*.<sup>15</sup>

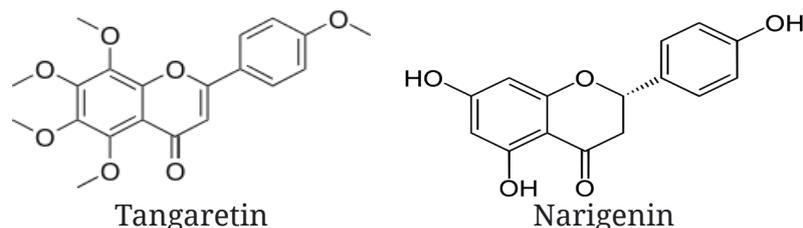


FIGURE 6. Flavonoids isolated from *Curcuma* spp.

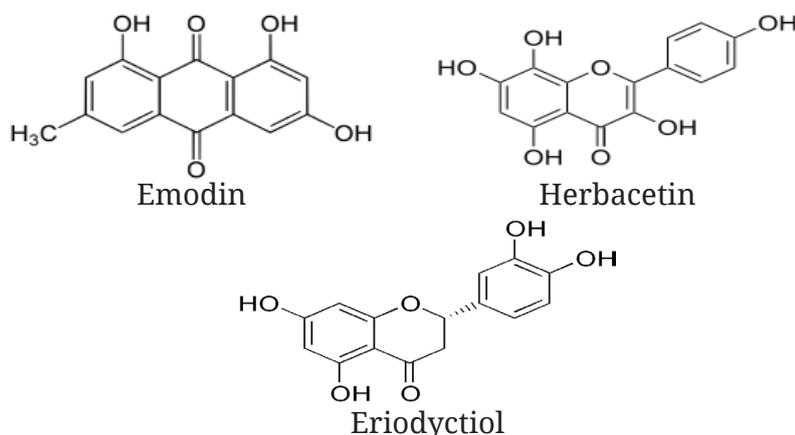


FIGURE 7. Emodin isoalted from *R. officinale*, herbacetin from *Citrus* spp. and eriodyctiol

ACE2 receptor serves as a gateway for SARS-CoV-2. This transmembrane protein is found on the cell surface of various tissues such as the nasal mucosa, lung parenchyma, digestive tract and kidneys, vascular endothelium, lymphoid tissue, reproductive system, and cerebral neurons which theoretically can provide viral access to several organs.<sup>3</sup>

A study using a supercomputer-based *in silico* drug-docking method against the SARS-CoV-2 virus S protein showed the identification of the

polyphenol quercetin as an ACE2 ligand, which can interfere with virus-host interactions.<sup>16</sup> The anthraquinone-type polyphenol, emodin (FIGURE 7), found in the roots of rhubarb (*Rheum officinale*) interferes with the interaction of the ACE2-S protein in a test study with an IC<sub>50</sub> of 200 mM. The same study also revealed that emodin reduced infection of Vero E6 cells expressing ACE2 by S protein-pseudo-typed retrovirus. These results indicate competition in the protein S receptor binding domain (RBD). Emodin

emerged as one of the 16 most usable agents for COVID-19 with low side effects and highest target specificity.<sup>17</sup>

A study using molecular docking methods and dynamic simulation studies predicts that polyphenols from plants such as Citrus and Curcuma species have a potential inhibitory effect on SARS-CoV-2 infection by interacting with the protein S RBD. Epigallocatechin gallate from tea plants, and herbacetin (FIGURE 8) from *Rhodiola* spp. (gold root) and other flavonoids also interact strongly with protein S RBD *in silico*.<sup>18</sup>

A molecular docking study using a computational model of the SARS-CoV-2 Spike protein interacting with the human ACE2 receptor found that the polyphenol compound eriodictyol (FIGURE 7), a flavanone found in yerba santa (*Eriodictyon californicum*) has one of the greatest binding affinities for the human ACE2 receptor moiety. Polyphenols can reduce SARS-CoV-2 viral infection by binding to ACE2 receptors, preventing viral entry, and reducing the severity of lung injury associated with COVID-19 by regulating ACE2 expression.<sup>19</sup>

Another study showed that polyphenolic compounds have the potential to inhibit the RNA-dependent RNA polymerase (RdRp) of SARS-CoV2. The inhibitory potential of SARS-CoV-2 RdRp by polyphenols is based on evidence that resveratrol significantly inhibits MERS-CoV replication *in vitro* by inhibiting RNA expression and nucleocapsid protein expression. Such evidence suggests that resveratrol may also be effective against SARS-CoV-2 infection.<sup>20</sup>

Fenoterol which is a polyphenol  $\beta$ 2-adrenergic receptor agonist, as well as the natural flavone baicalin (FIGURE 8) from *Scutellaria baicalensis* and several xanthenes from *Swertia apseudochinensis* were identified as potential RdRp inhibitors of SARS-CoV-2 by computational methods. Another *in silico* study recently reported that epigallocatechin gallate, myricetin, quercetagein (FIGURE 8) and other polyphenols exhibit high binding affinity to the RdRp of SARS-CoV and SARS-CoV-2.<sup>21</sup>

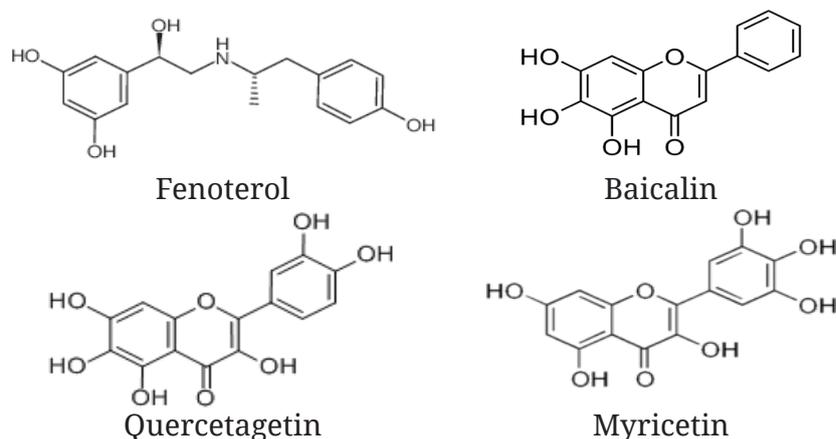


FIGURE 8. Polyphenol isolated from *S. baicalensis* and *S. apseudochinensis*

### Limitations of the study

Thousands of polyphenol compounds belonging to various groups of bioactive compounds have been isolated from the natural ingredients. This review of the literatures demonstrated that some of the

polyphenol compounds exhibit potential activity against SARS-CoV-2. However, most of the studies are conducted *in silico* or *in vitro* using cell lines. As new virus, no *in vivo* studies using animal models infected by the SARS-CoV-2 have been

conducted. Therefore, the development of the animal models for pre-clinical studies are required.

Furthermore, several pre-clinical studies should be conducted including solubility and stability of the chosen polyphenol, initial pharmacokinetics and pharmacodynamics in animal model, mechanism of action studies in suitable animal models, preliminary toxicology studies that enable approximations as to therapeutic indices.<sup>22</sup> From these pre-clinical studies conclusions can be made as the possible further clinical studies.

## CONCLUSION

Polyphenols are large group of active compounds found in the medicinal plants. Thousands of the polyphenol have been isolated and proven their biological activity against various pathogen infections including viral infection. During COVID-19 pandemic, various the polyphenols have been investigated for their activity and mechanism of actions against SARS-CoV-2. Among the polyphenols investigated, some of them namely papyriflavonol, catechin gallate, gallic acid, luteolin, quercetin, tangeretin, naringenin, herbacetin, emodin, eriodictiol, fenoterol, baicalin, myricetin, quercetagenin exhibited strong activity against SARS-CoV-2 with several mechanism of actions included 1) bind to the N protein causing the inhibition of viral transcription and replication; 2) inhibit the binding of S protein to ACE2 receptors preventing the entry of the virus into the host cells; 3) inhibit 3CL<sup>pro</sup> function inhibiting the viral transcription and maturation; and 4) bind directly to the ACE2 receptor. However, most of these studies still conducted *in silico* or *in vitro*. Further the pre-clinical and clinical studies are required to strengthen existing evidence.

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