Ahmad Fadhil Ilham-Potential of Emodin as Effective Therapy Overcoming COVID-19 through Inhibition of the SARS-CoV-2 Spike Protein Interaction on ACE2 Receptors

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Potential of Emodin as Effective Therapy Overcoming COVID-19 through Inhibition of the SARS-CoV-2 Spike Protein Interaction on ACE2 Receptors

Abstract

Background: *Coronavirus disease 2019 (COVID-19) was a huge pandemic to date. Patients in severe to critical conditions, especially with comorbidities tend to have complications, such as ARDS, cytokine storm, etc, have higher mortality, and need more effective treatment. Emodin is a candidate regimen that has the potential benefit for COVID-19.*

Methods: *This literature review was synthesized in detail and systematically, with literature searches on journal databases such as PubMed, ScienceDirect, EMBASE, and the Google Scholar search engine. As a result, three main literatures and 27 supporting literatures were found which were used to synthesize this literature review.*

Results: *Pathogenesis of SARS-CoV-2 infection was similar to SARS-CoV infection, as demonstrated by Hoffmann et al., namely through the interaction of viral spike (S) protein with ACE2 receptors in the human body, so the inhibition of this interaction would be one of therapeutic target. Ho et al. proved that emodin can inhibit the binding of the SARS-CoV S protein to ACE2 in vitro. The direct inhibition of S protein may also support the required cardioprotective function of ACE2 in patients with cardiovascular comorbidities. Emodin is also superior because it has various other benefits such as anti-inflammatory and immunosuppressive activity. Based on the research of Dong et al., emodin can be given orally but in combination with inhibitors of glucuronidation metabolism can increase the bioavailability of this drug.*

Conclusion: *Emodin has the potential to be developed for the effective therapy of COVID-19.*

Keywords: *COVID-19, SARS-CoV-2, emodin, spike protein, ACE2 receptor*

Potensi Senyawa Emodin sebagai Terapi Efektif Atasi COVID-19 Melalui Inhibisi Interaksi Protein *Spike* SARS-CoV-2 Terhadap Reseptor ACE2

Abstrak

Latar belakang: *Coronavirus disease 2019 (COVID-19) merupakan pandemi terbesar hingga saat ini. Pasien derajat berat dan kritis terutama dengan komorbid lebih mudah menimbulkan komplikasi seperti ARDS, badai sitokin, dll, serta memiliki risiko kematian lebih tinggi sehingga membutuhkan terapi yang lebih efektif. Emodin menjadi salah satu kandidat regimen yang berpotensi digunakan untuk terapi efektif COVID-19.*

Metode: *Kajian literatur ini disusun secara rinci dan sistematis, dengan pencarian literatur pada database jurnal seperti PubMed, ScienceDirect, EMBASE, serta mesin pencari Google Scholar. Hasilnya didapatkan tiga literatur utama dan 27 literatur pendukung yang digunakan untuk sintesis kajian literatur ini.*

Hasil: *Patogenesis SARS-CoV-2 memiliki kesamaan dengan infeksi SARS-CoV ditunjukkan oleh penelitian Hoffmann dkk, yakni melalui interaksi protein spike (S) virus dengan reseptor ACE2 pada tubuh manusia, sehingga inhibisi interaksi tersebut berpotensi menjadi sasaran terapi. Penelitian Ho dkk membuktikan emodin dapat menghambat ikatan protein S SARS-CoV terhadap ACE2 secara in vitro. Potensi inhibisi langsung pada protein S juga dapat mendukung fungsi kardiprotektif ACE2 yang diperlukan pada pasien dengan komorbiditas kardiovaskular yang menjadi salah satu kontributor utama angka kematian akibat COVID-19. Emodin juga bersifat unggul karena memiliki berbagai manfaat lainnya seperti antiinflamasi dan aktivitas imunosupresif. Berdasarkan penelitian Dong dkk, emodin dapat diberi secara oral namun kombinasi dengan inhibitor metabolisme glukoronidasi dapat meningkatkan bioavalabilitas obat ini.*

Kesimpulan: *Emodin berpotensi dikembangkan untuk terapi efektif COVID-19.*

Kata kunci: *COVID-19, SARS-CoV-2, emodin, spike protein, ACE2 receptor*

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a pandemic health problem that has caught the attention of people around the world to this day.[1,2] The total accumulation of cases and the number of deaths from COVID-19 continues to increase over time. The high mutation rate of the virus also causes the formation of new variants so this problem remains unresolved.[2-4]

The spread of the SARS-CoV-2 virus is very fast compared to other coronaviruses. People with COVID-19 can experience various complaints such as fever, cough, sore throat, and headache.[2,5,6] This infection could elicit immune response and then lead to pneumonia, cytokine storms, and also acute respiratory distress syndrome (ARDS). COVID-19 patients with comorbidities also had more complications such as sepsis or multiple organ failure (MOF). The worsening condition of COVID-19 accompanied by various complications can cause death in patients, so the management is important.[2,6,7]

Until now, many studies were developed in order to find effective treatments for COVID-19. Although the pathogenesis is not fully understood, various studies have shown the pathogenesis of SARS-CoV-2 infection is similar to the pathogenesis of SARS-CoV infection, which is related to the binding between the spike protein (S) on the virus and the angiotensin-converting enzyme 2 (ACE2) receptor in the human body. This binding helps the virus enter the cells and replicate, then trigger the immune system that could destroy the body.[2,8-10]

Regarding this pathogenesis, many studies were developed to find effective treatments. Emodin is an anthraquinone derivative compound that can be found in various herbs of the *Rheum* and *Polygonum* genera. Some studies have shown evidence of emodin compounds having the ability to inhibit the interaction between the spike (S) protein in the SARS-CoV virus and the ACE2 receptor. In addition, emodin is also thought to have the ability to support the protective function of ACE2 which is beneficial for the body and is needed by groups of patients with cardiovascular comorbidities that become one of the main contributors to mortality rates.[10,11]

Based on the benefits of emodin and the similarities between SARS-CoV and SARS-CoV-2 infectious pathogenesis, the authors were prompted to demonstrate the potential use of emodin in COVID-19 cases. Therefore, this literature review aims to discuss the role of emodin as an effective therapy to overcome COVID-19 and reduce its mortality rate to solve the current pandemic problem.

METHODS

This literature review is synthesized in detail and systematically. The authors conducted a literature search using various journal databases such as PubMed, ScienceDirect, and EMBASE as well as the Google Scholar search engine with keywords: "COVID-19", "SARS-CoV-2", "emodin", "spike protein", and “ACE2 receptor”. As a result, three main literatures were critically reviewed in this study, namely the studies of Ho et al., Hoffmann et al., and Dong et al. In addition, 27 supporting literatures were also obtained which were used in this literature review to analyze and support the results of the three main articles.

RESULTS AND DISCUSSION

Current Challenges of the COVID-19 Pandemic

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by the SARS-CoV-2 virus which is part of the Coronavirus group. The SARS-CoV-2 virus has a genome structure in the form of a pattern similar to other coronaviruses, including an open reading frame, envelope, membrane, nucleocapsid, and spike.[12,13] Until now, COVID-19 is still a pandemic challenge and Indonesia is no exception because the total number of cases and deaths continues to grow over time. The immune system response could become out of control and continue with cytokine storm, ARDS, and MOF. Comorbidities also influenced severity and mortality.[2,6] The rapid spread of the virus increased number of cases, morbidity, the presence of complications, and mortality. Therefore many studies

were developed to look for effective treatment and prevention, but only corticosteroids showed benefit.[2,6,7,14]

Spike Protein Interaction with ACE2 Receptors as Key Pathogenesis

The pathogenesis of COVID-19 remains not fully understood, even though it was suspected similar to the pathogenesis of SARS-CoV infection that has been studied previously.[2,8,9] Based on computer modeling, there was a three-dimensional structure of the spike protein with receptor-binding domains in SARS-CoV-2 similar to those found in SARS-CoV. This protein in SARS-CoV has a strong affinity for the ACE2 receptor, while an in vitro data on SARS-CoV-2 also supports the alleged use of the ACE2 receptor by this virus.[2,13,15]

The similarity in the pathogenesis of the SARS-CoV and SARS-CoV-2 viruses through the same receptor, ACE2, was also demonstrated by Hoffmann et al.[16] who tested the receptor for the entryway of various viruses in a cultured cell named BHK-21. The results showed that both SARS-CoV and SARS-CoV-2 viruses used human and bat-derived ACE2 receptors (hACE2 and batACE2) without affecting the hAPN receptor used by the HCoV-299E virus and the DPP4 receptor used by MERS-CoV significantly.[16]

SARS-CoV-2 primarily infects the cells of the respiratory tract lining the alveoli. Based on studies on SARS-CoV, S protein has an important role in the entry of viruses into cells. With the glycoprotein structure of the S protein, the virus can bind to the ACE2 receptor.[2,9] Furthermore, SARS-CoV-2 with the help of the TMPRSS2 enzyme enters cells and carries out a replication process that ultimately damages the body by triggering an increase in the body's immune system that leads to pneumonia, ARDS, and other disorders.[2,17,18]

Treatment Potential with Inhibition of S Protein Interaction with ACE2 Receptors

The COVID-19 pathogenesis is closely related to the interaction of viral S protein with the ACE2 receptor, making it a potential therapeutic target. Inhibiting the interaction between S protein and ACE would make the virus cannot enter the cell so that viral replication does not occur. Various regimens whose mechanism is similar to the target pathogenesis have been investigated, such as hydroxychloroquine and chloroquine phosphate which inhibit ACE2 receptor glycosylation which in turn causes the interaction of the agent and receptor to be reduced. These drugs showed good results in in vitro studies, so the research was developed to clinical trials.[19] The existence of drug potential in the development of research with this mechanism makes the application of drugs with inhibition of S protein interaction with ACE2 more convincing. However, there were randomized clinical trials and systematic reviews that showed hydroxychloroquine and/or chloroquine phosphate alone gave unsatisfactory results when applied to patients, so we need to evaluate other important candidate regimens.[20-23]

Compared with hydroxychloroquine and chloroquine phosphate which inhibit ACE2 receptors directly, interaction inhibition was thought to be more effective when inhibition was carried out on S protein. This statement is based on ACE2 which has a protective function in the body, that could convert angiotensin II to angiotensin 1-7 which can reduce hypertension, cardiac fibrosis, thrombus, and ARDS. This protective function makes it considered a targeted therapy not to inhibit and reduce the ACE2 receptor itself, but rather to target the inhibition of viral binding to the receptor so it is hoped that the protective function of ACE2 will not be disturbed.[10]

The Benefit of S Protein Interaction Inhibition in Patients with Cardiovascular Comorbidities

The inhibition mechanism of the S protein interaction on the ACE2 receptor would also play a very important role among COVID-19 patients who have cardiovascular comorbidities. It is known that susceptible patients with cardiovascular comorbidities have a high risk of experiencing severe COVID-19 that requires intensive care, such as respiratory failure or hemodynamic failure.[10,24] Chen et al.[25] study showed that 40% of hospitalized patients with COVID-19 had cardiovascular or

cerebrovascular disease and Wang et al.[26] showed 31% of hypertensive patients and 14.5% of patients with cardiovascular disease in 138 COVID-19 patients.[24-26]

Angiotensin-converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB) regimens were first-line treatment for hypertension with cardiovascular. A study by Ferrario et al.[24] showed that both ACEI and ARB regimens could significantly increase the expression of cardiac ACE2 mRNA which plays a protective role. This was related to the previous statement that inhibition of the ACE2 receptor itself as an effort to inhibit the interaction of the virus with the receptor is an ineffective mechanism because it interferes with cardioprotective function which is actually important for patients with cardiovascular comorbidities.[10,24] Therefore, the mechanism of inhibition of S protein as a target is more promising to support this protective function, so it is hoped that this inhibitory therapy can also benefit patients with cardiovascular comorbidities, which are one of the major contributors to mortality.

Emodin as a Promising Compound for COVID-19 Therapy

Emodin is an anthraquinone derivative which is the content of various traditional herbs that have been widely used as traditional medicine in East Asia, including *Rheum officinale, Rheum palmatum, Polygonum multiflorum, Polygonum cuspidatum, Cassia obtusifolia,* and *Aloe vera*. Emodin is a 9,10-anthraquinone compound with substitution of hydroxy groups at positions 1,3, and 8 and a methyl group at position 6. Emodin or 1,3,8-trihydroxy-6-methylanthraquinone has the molecular formula of $C_{15}H_{10}O_5$.[11-13,27]

Ho et al.[11] have investigated the role of emodin compounds against SARS-CoV infection in vitro. Initially, Ho et al.[11] conducted a test to see the effect of various traditional herbal extracts on the binding of S protein to ACE2. In this test, Ho et al.[11] used a solution of herbal extract and S protein labeled with biotin which was added to wells containing ACE2. The ELISA test was used to determine the absorbance and based on certain calculations, the percentage of the herbal extract inhibition on S protein binding associated with ACE2 could be determined.[11]

Screening 312 medical herbs which were divided into 32 families found that 25 families were able to eliminate the interaction of S protein with ACE2. Among these 25 families, *Polygonaceae* family produced the highest inhibition activities (86.33%). *Polygonaceae* family studies showed there were root tubers of *Rheum officinale* (*Rheum* genus) called Radix et Rhizoma Rhei and root tubers and vine stems of *Polygonim multiforum* (*Polygonum* genus) called Radix Polygoni multiflori and Caulis Polygoni multiflori. In preincubation of herbs with biotin-labeled S protein, the three samples showed similar results, namely the binding of S protein to ACE2 was inhibited.[11]

Herbs of the *Rheum* and *Polygonum* genera also were known to have high content of emodin and rhein which are anthraquinone compounds and chrysin which is a flavonoid. Based on this statement, Ho et al.[11] investigated the role of these compounds in inhibiting the binding of S protein to ACE2 using herbal extracts methods but replaced the herbal extracts with these pure compounds. This study found that emodin compound could inhibit the binding of S protein to ACE2 which was consistently in line with increasing the number of doses.[11]

The inhibition increased with the increase in the concentration of the emodin compound and this result was similar to the results shown in the test with the three previous herbal extracts. It was found that the IC50 value of emodin was 200 μM. Meanwhile, different results were obtained for other compounds. Assays on rhein produced less and inconsistent interaction inhibition, while assays on chrysin produced weak inhibition at 400 μM and even stimulated binding of S protein to ACE2 at 50 μM. With these results, emodin became the active compound in plants of the *Rheum* and *Polygonum* genera. which is thought to have a role in inhibiting the binding of S protein to ACE2, while other compounds did not show this effect.[11]

In addition to antiviral effects, various studies

have demonstrated the pharmacological effects of emodin, such as anti-inflammatory through inhibition of the NF-kB pathway and immunosuppressive activity by inhibiting the growth of certain immune cells. Emodin also has antitumor, antibacterial, antiallergic, antidiabetic, antiosteoporotic, hepatoprotective, and neuroprotective properties which make it potential in the therapy of patients with comorbidities such as atherosclerosis, cancer, asthma, atopic dermatitis, diabetes, osteoarthritis, hepatic disease, Alzheimer's, and others.[28,29] A summary of the potential and considerations of emodin as a COVID-19 therapy can be seen in Figure 1.

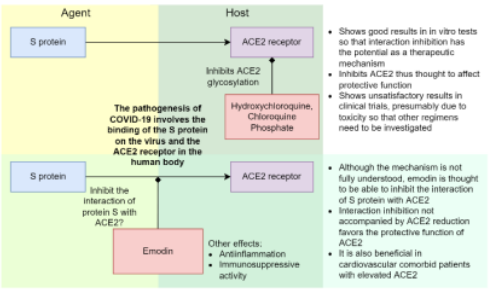

Figure 1. Potential of emodin as a COVID-19 therapy and its comparison with hydroxychloroquine and chloroquine phosphate.

So far, the use of emodin compounds is carried out orally in the form of traditional herbs containing emodin, while the administration of pure compounds as drugs has not been widely applied. Dong et al.[28] showed that the administration of emodin can be done orally, but the bioavailability of this compound is still relatively low due to phase II metabolism in the form of glucuronidation which forms glucuronides and causes drug inactivation. Therefore, the pharmacokinetics of emodin need to be improved with a combination of glucuronidation metabolism inhibitor agents, so that the drug bioavailability and efficacy increase.[28,30]

CONCLUSION

COVID-19 remains a problem especially for patients with comorbidities. The pathogenesis of this infection was similar to that of SARS-CoV infection, which uses viral S protein and the ACE2 receptor as a pathway of entry, therefore inhibition of this binding could be a targeted therapy. In vitro study showed that emodin compounds could inhibit those binding. The technical application of emodin therapy is still under research, but oral administration with a combination of glucuronidation inhibitors has good potential to be applied in clinical practice. Therapy with emodin has been proven to be superior in the management of COVID-19 because it has the potential to inhibit the binding of S protein to ACE2, supports the protective function of ACE2 in the body, is beneficial for patients with cardiovascular comorbidities, even the clear mechanism of the pharmacodynamics of emodin were still unknown. Emodin also has anti-inflammatory and immunosuppressive activity. Therefore, emodin is a strong agent candidate as a solution for the morbidity and mortality problems in the current pandemic.

The limitation of this literature review is the study of emodin as a COVID-19 therapy was still very limited. Therefore, this review recommends further research on the effect of emodin compounds as a COVID-19 therapy from preclinical to clinical trials. It is also important to evaluate another protective effect of emodin.

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