Literature Review

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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Abstract

Background: The coronavirus disease 2019 (COVID-19) once became a major pandemic in the history of human health. Patients in severe to critical conditions, especially with comorbidities, are more likely to have complications such as ARDS, cytokine storm, higher mortality rates, and require more effective treatments. Emodin is a candidate regimen that has the potential benefit for COVID-19.

Method: This literature review was synthesized with literature searches on journal databases such as PubMed, ScienceDirect, EMBASE, and the Google Scholar search engine. As a result, three main articles and 36 supporting articles were used to synthesize this literature review.

Results: The 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 the therapeutic targets. 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 ACE2 cardioprotective function 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: ACE2 receptor, COVID-19, emodin, SARS-CoV-2, spike protein

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) is caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and has become a global health problem, capturing the attention of people worldwide.[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 was very rapid during the pandemic.[2,5] People with COVID-19 can experience various complaints such as fever, cough, sore throat, and headache.[2,5,6] This infection can elicit an 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 management is important.[2,6,7]

Until now, many studies have been developed 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 Severe Acute Respiratory Syndrome Coronavirus (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 triggers 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 (Figure 1). 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”.

The inclusion criteria are: (1) articles that are research studies, reviews, and official global or national institutions reports, (2) published within the last five years, except for key discussions specifically on SARS-CoV and emodin in the review, and (3) full-text availability. The exclusion criteria are: (1) articles in the form of editorials or comments.

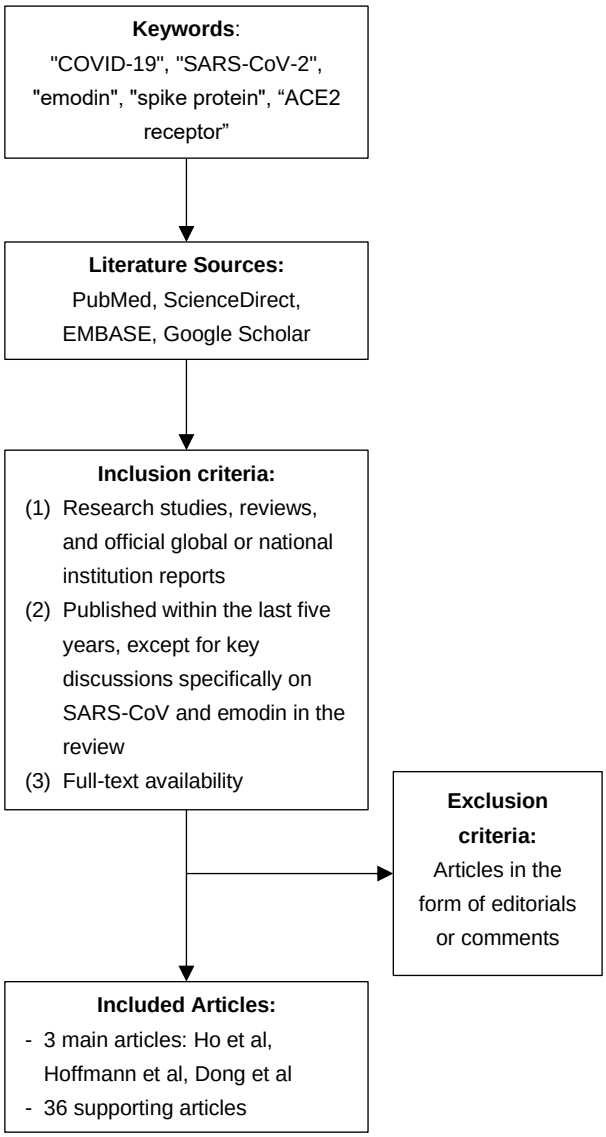

Figure 1. Study flow chart

RESULTS

As a result, three main articles were critically reviewed in this study, namely the studies of Ho et al, Hoffmann et al, and Dong et al. The literature review was conducted through the evaluation, analysis, and interpretation of data.

Table 1. Summary of Main Findings

Main Article	Findings	Supporting Articles
Ho et al[11]	• Emodin, extracted from the Rheum and Polygonum genera, effectively inhibited the binding of the spike protein to ACE2. • Highlights the potential of emodin as a therapeutic agent against COVID-19 that may be applied clinically by preventing viral entry into host cells.	Guo et al, Zhu et al, Zhou et al, Zhang et al, Nejat et al, Li et al, Kuo et al, Naz et al, Ma et al, de Oliveira et al, Muchtaridi et al, Dong et al, Stompor-Gorący et al, Chen et al[10,12–25]

Main Article	Findings	Supporting Articles
Hoffmann et al[26]	• Demonstrated that both SARS-CoV and SARS-CoV-2 could use human ACE2, confirming its critical role in COVID-19 pathogenesis. • Emphasized the need to target the spike protein-ACE2 interaction for therapeutic interventions. • Indicates drug targets for further development to enable clinical application.	Handayani et al, Susilo et al, WHO Report, Indonesian Government Report, Huang et al, Guan et al, Zhou et al, Zhang et al, Li et al, Guo et al, Zhu et al, Zhou et al, Li et al, Xiao et al, Zhu et al, Li et al, Groß et al, Borba et al, Das et al, Singh et al, Singh et al, Beyerstedt et al, Ferrario et al, Chen et al, Wang et al, National Center for Biotechnology Information[1–10,12,13,27–39]
Dong et al[23]	• Emodin exhibits antitumor, antibacterial, antiallergic, antidiabetic, antiosteoporotic, hepatoprotective, and neuroprotective properties. • The oral bioavailability of emodin may be enhanced by combining it with inhibitors of glucuronidation metabolism, thereby improving its therapeutic efficacy. • Emodin has the potential to be developed into a therapeutic agent for daily clinical practice.	Guo et al, Zhu et al, Zhou et al, Zhang et al, Nejat et al, Li et al, Kuo et al, Naz et al, Ma et al, de Oliveira et al, Muchtaridi et al, Dong et al, Stompor-Gorący et al, Chen et al[10,12–25]

In addition, 36 supporting articles were also obtained which were used in this literature review to analyze and support the results of the three main articles (Table 1).

DISCUSSION

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by the SARS-CoV-2 virus, 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 increase. 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 the 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.[2,6,7,27] The main important findings from this literature review are presented in Table 1, with a detailed discussion provided in the subsequent subsections.

The pathogenesis of COVID-19 remains not fully understood, even though it is 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 in vitro data on SARS-CoV-2 also supports the alleged use of the ACE2 receptor by this virus.[2,13,28]

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 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.[26]

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.[2,29,30]

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 unable to 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 into clinical trials.[31]

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. For example, there was no significant difference in health outcomes, such as viral clearance, between administering hydroxychloroquine and not administering it, and some studies even showed an increase in mortality with hydroxychloroquine. Therefore, it is necessary to evaluate other important candidate regimens.[32–35]

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.[10,36]

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.[10,37] Chen et al study showed that 40% of hospitalized patients with COVID-19 had cardiovascular or cerebrovascular disease.[38] And, Wang et al showed 31% of hypertensive patients and 14.5% of patients with cardiovascular disease in 138 COVID-19 patients.[37–39]

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 showed that both ACEI and ARB regimens could significantly increase the expression of cardiac ACE2 mRNA which plays a protective role.[37]

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 important for patients with cardiovascular comorbidities.[10,37] 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 is an anthraquinone derivative that 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 cupsidatum, Cassia obtusifolia,* and *Aloe vera*. Emodin is a 9,10-anthraquinone compound with hydroxy group substitutions 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 $C_{15}H_{10}O_5$.[11–14]

Ho et al have investigated the role of emodin compounds against SARS-CoV infection in vitro. Initially, Ho et al conducted a test to see the effect of various traditional herbal extracts on the binding of S

protein to ACE2.[11] In this test, Ho et al used a solution of herbal extract and S protein labeled with biotin which was added to wells containing ACE2.[11] 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.[11,16]

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%).[11,17] *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.[11,18]

Herbs of the *Rheum* and *Polygonum* genera also were known to have a high content of emodin and rhein which are anthraquinone compounds and chrysin which is a flavonoid.[11,19] Based on this statement, Ho et al 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.[11] 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.[11,20]

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.[11] 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.[11,21] 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.[11,22]

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.[23,24]

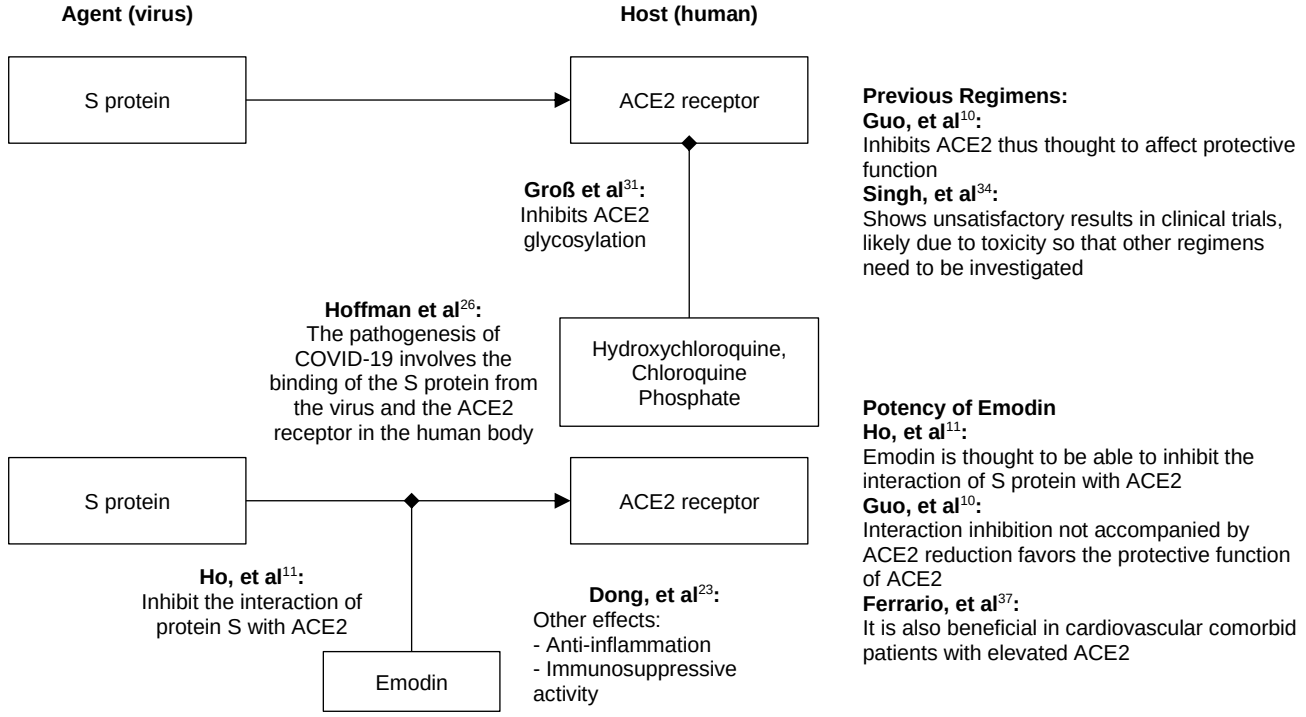

Figure 2. Summary of key studies regarding the potential of emodin as a COVID-19 therapy

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.[23,24] A summary of the potential and considerations of emodin as a COVID-19 therapy can be seen in Figure 2.

To date, the use of emodin compounds has been predominantly limited to oral administration in the form of traditional herbal preparations containing emodin, while the application of pure emodin compounds as pharmaceutical agents remains largely unexplored. Dong et al 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.[23,25]

CONCLUSION

COVID-19 continues to pose challenges, especially in 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.

Emodin has shown potential as a COVID-19 therapy, with favorable results from in vitro studies demonstrating its ability to inhibit binding. Additionally, oral administration combined with glucuronidation inhibitors appears to have potential for clinical use. Emodin therapy is considered advantageous in managing COVID-19 due to its ability to inhibit the binding of the S protein to ACE2, support the protective function of ACE2 in the body, and benefit patients with cardiovascular comorbidities. Moreover, emodin exhibits anti-inflammatory and immunosuppressive properties. Therefore, emodin is a strong candidate for addressing the morbidity and mortality challenges.

As a recommendation, this literature review can serve as a foundation for the continued development of emodin therapy for COVID-19, with future directions starting from in vivo laboratory tests, followed by phased clinical trials, and eventually, operational tests to assess its practical feasibility. It is also important to evaluate other potential protective effects of emodin to ensure its benefits can be more effectively applied in everyday life.

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CONFLICT OF INTEREST

None.

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