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The Utilization of Nutraceuticals and Phytochemical Compounds to Inhibit The Interaction of Spike-protein SARS-CoV-2 Virus and ACE-2 Receptor for COVID-19 Therapy (Literature Review)

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Abstract

SARS-CoV-2 virus can cause Coronavirus disease 2019 (COVID-19). The interaction between spike protein and ACE2 receptor causes virus entry into the cells. The aim of this study was to review the utilization of nutraceutical and phytochemical agents to inhibit the interaction of spike protein envelope SARS-CoV-2 virus and ACE2 receptor. The data literature was retrieved from several databases such as Google scholar, Science direct, and PubMed. This study was conducted from September-October 2020. The review process was conducted based on PRISMA Guidelines.The results showed that nutraceuticals such as tuna peptides (EEAGGATAAQIEM), nisin, teicoplanin, zinc, propolis, *Ganoderma lucidum*, brown algae, and lectin have the potential to inhibit the interaction of spike protein SARS-CoV-2 virus and ACE2 receptor. Phytochemical compounds such as curcumin, luteolin, EGCG, hesperidin, resveratrol, saikosaponin, nicotianamine, procyanidin and the others also have the same. From this study, it can be concluded that nutraceuticals and phytochemical agents have potential benefits in COVID-19 treatment based on in silico study. However, we need further studies based on in vitro experiments and in vivo to ensure the effectivity of those nutraceutical agents.

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Introduction

SARS-CoV-2 is a new virus that was discovered in December 2020 (Huang et al., 2020). The first infection case was reported in several patients in Wuhan, Hubei Province, China with symptoms like pneumonia. The SARS-CoV-2 virus can spread rapidly (Helmy et al., 2020). The transmission of SARS-CoV-2 virus into human body can cause Coronavirus Diseases 2019 or COVID-19 (Bourgonje et al., 2020). The common symptoms of COVID-19 are cough, fever, shortness of breath and also death caused by pneumonia (Tosepu et al., 2020). Nowadays, more than 200 countries were infected by the SARS-CoV-2 virus (Helmy et al., 2020). Due to these problems, COVID-19 has become a global pandemic cases (Asyary and Veruswati, 2020).

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There is no specific antiviral for SARS-CoV-2 virus. So, the drug development that specific to this virus is urgently needed to overcome this pandemic (Ansori et al., 2020).

In order to develop COVID-19 drugs, we must understand the life cycles of SARS-CoV-2 virus (Saxena, 2020). The initial process of SARS-CoV-2 virus infection is the interaction between spike protein and ACE2 receptor that make this virus enter the cells (Jeong et al., 2020). The interaction affinity between the SARS-CoV-2 virus spike protein and the ACE2 receptor is very high (Cohen et al., 2020). Thus, SARS-CoV-2 virus spike protein is a major key in the development of vaccines and antiviral drugs (Ansori et al., 2020). Unfortunately, SARS-CoV-2 virus is composed of a single stranded RNA that makes the process of RNA-proof reading occur incompletely that led to the mutation (Helmy et al., 2020).

Based on the article published by ECDC (2020), it was explained that the presence of the SARS-CoV-2 virus mutation in the United Kingdom could affect the protein spike. The mutation process occurs due to deletions in amino acids P681H, A570D, S982A, D1118H, T7161, 114, N501Y, D614G, and deletions in amino acids 69-70 can increase the transmission power of the virus up to 70% that cause the cellular infection process also increases. Based on previous research conducted by Khan et al (2020), there are 13 different SARS-CoV-2 mutant viruses in several countries including Italy, Australia, Finland, South Korea, China, Nepal, Vietnam, Brazil, Japan, India, US, Taiwan and Sweden. That study found that the mutation process can cause changes to the SARS-CoV-2 spike protein, especially in virus mutants originating from Australia (247 position, serine → arginine), South Korea (221 position, serine → tryptophan), India (408 position, arginine → isoleucine), Finland (49 position, histidine → tyrosine), and Sweden (797 position, phenylalanine → cysteine). The presence of mutations can increase the stability of the RBD-spike protein.

Ansori et al (2020), in their research carried out the process of identifying the genome sequences of each type of mutant SARS-CoV-2 virus in Indonesia by accessing the Genbank database and GISAID EpiCoV. The results of the identification of genomic sequences showed that 10 mutant types of SARS-CoV-2 virus were found in Indonesia including the main virus (Wuhan-Hu-1), JKT-EIJK0141, JKT-EIJK0317, JKT-EIJK2444, EJ-ITD853Sp, EJ-ITD3590NT, JKT - EIJK01, JKT-EIJK02, JKT-EIJK03, and JKT-EIJK04. The results of each viral genome sequence will determine the site of mutation both in the nucleotide and amino acid sections. The results showed that each type of virus mutant had a similarity level of 99.9% -100%. The study explained that the mutation did not significantly affect the spike protein activity so that the protein spike was the main target site in the development of vaccines and drugs for COVID-19. Therefore, spike protein was chosen as the target site because the mutation only affects the stability of the RBD-spike and does not significantly affect changes in the target site of the vaccine or drug candidate.

Several of the drugs that are used for COVID-19 therapy are chloroquine (CQ) and hydroxychloroquine (HCQ). These drugs can inhibit the interaction between spike protein and ACE2 receptors (Sinha and Balayla, 2020). The mechanism of action of CQ and HCQ is increasing the pH (alkalization) of the endosomes and lysosomes of the cells so that the SARS-

CoV-2 virus cannot fuse into the cell membrane. In addition, CQ can also interfere with the glycosylation process of cell receptors (Drozdal et al., 2020). Unfortunately, CQ and its derivatives have side effects such as nausea, vomiting, diarrhea, headaches, dizziness, seizures, disturbances of taste and smell, and tinnitus. In long-term use, CQ and HCQ can cause retinopathy and cardiopathy due to the toxic effects of these drugs (Zou et al., 2020). Therefore, it is necessary to have an alternative therapy.

Nutraceutical is a type of therapy used to prevent and treat chronic diseases such as diabetes, heart disease, neurodegenerative, respiratory disorders, and so on. Nutraceutical is a product developed from a variety of processed ingredients including minerals, foodstuffs, herbs, and natural derivatives based on very strict specification requirements (cGMP) to ensure the effectiveness of therapy (Pathak, 2010). The advantages of nutraceuticals are relatively more economical and safer costs due to its lower side effects compared to synthetic drugs (Gil et al., 2016). In addition, the use of nutraceuticals during a pandemic also has an important role in maintaining body health and preventing the transmission of the SARS-CoV-2 virus (Matteo et al., 2020). Nutraceuticals also contains phytochemical components that can significantly provide benefits for the health of the body (Sharma, Prakash, and Gupta, 2014). Therefore, this research will conduct a literature review process related to the use of nutraceuticals and phytochemical components that can inhibit the interaction between the SARS-CoV-2 virus spike-protein envelope and the ACE2 receptor for COVID-19 therapy.

Materials and Methods

Literature Search

In this study, the literature search was conducted by using several search engines: Google Scholar (https://scholar.google.com), Science Direct (http://www.sciencedirect.com/), and PubMed (http://www.ncbi.nlm.nih.gov/pubmed). The literature search process was done using several of keywords combination: ["COVID-19", "SARS-CoV-2", "ACE2", "*spike protein*", "*nutraceutical*"] *AND* ["COVID-19", "SARS-CoV-2", "ACE2", "*spike protein*", "*plant*"] *AND* ["COVID-19", "SARS-CoV-2", "ACE2", "*spike protein*", "*food*"]. The search process was occurred in September and October 2020. The filters of literature search were: years (2020) and language (English).

Screening Literature

The literature for searching process was then screened to eliminate duplication. Then, the literature was screened through several criteria of inclusion: international journal; English language; and article types (research or review). Also, this study used the exclusion criteria: Indonesian language, article type: commentary, news, opinion, or letter. The results of all these processes were documented carefully both its included and excluded data.

Eligibility Study

The eligibility study was conducted by screening the article deeply from its abstract, methodology, and results. Then, the literature was screened based on the relevance of data article and research topic. The excluded articles are documented with a reasons. Based on article by (Sharma, Prakash, and Gupta, 2014), it is explained that nutraceutical is a food

component that used to prevent and treat various kinds of chronic diseases. But, generally food ingredients also contain phytochemical compounds that significantly provide health benefits. Therefore, the process of inclusion data also carried both on nutraceutical and phytochemical with the consideration that COVID-19 is an urgent case.

Inclusion Data

The inclusion data from every literature process was reported briefly into a PRISMA diagram. Then the final data was also reported into table of summary. Data articles with a year of publication less than 2020 were also be used for supporting reference in the discussion section.

Results and Discussion

The results of the literature review process are systematically reported in the PRISMA flowchart and the number of articles accepted and rejected is recorded. The presentation of article data from a systematic study can be seen in Figure 1.

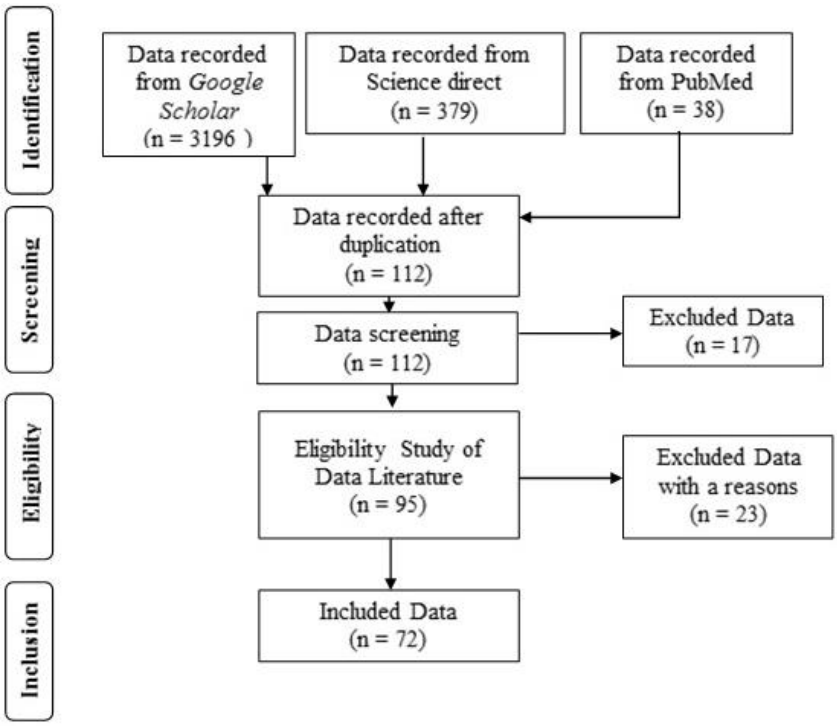

Figure 1. The Results of Literature Review Reported on PRISMA Diagram

From the results of the literature review, it was found that various types of nutraceuticals and phytochemicals that can be used for COVID-19 therapy can be explained as follows.

Phytochemical

Alkaloids

Based on in silico research conducted by Gyebi et al (2020), the following results were obtained: cryptopyrolepine (-10.7 kcal/mol), 10-hydroxysambaresine (-10.4 kcal/mol), and strychnopentamine (-9,9 kcal/mol). Besides, the study also explained that three alkaloid components were effective in binding ACE-RBD with their respective bond energies: -10.7

kcal/mol; -10.5 kcal/mol; and -10.5 kcal/mol (Gyebi et al., 2020). Other components such as bis-benzylisoquinoline alkaloids-tetrandine from the *Stephaniae Tetrandae* Radix plant can also suppress spike protein (Xian et al., 2020).

Amarogentin

Based on research conducted by Maurya et al. (2020), it was found that AG compounds can bind to spike glycoproteins very well seen from the docking score value of -149.76 kcal/mol where this component can form 9 hydrogen bonds in the residue amino acids Gln314, Ser735, Val736, Cys738, Thr739, Arg765, and Thr768.

Andrographolide (AGP)

Andrographolide (AGP) is a type of phytochemical component commonly found in *Andrographis paniculata* plants (Murugan et al., 2020). AGP has a broad spectrum antiviral effect because it can inhibit spike protein (-6.1 kcal/mol) and ACE2 (-6.8 kcal/mol) from the SARS-CoV-2 virus (Huang et al., 2020).

Artemisinin and Its Derivatives

The molecular docking test of the artemisinin compound and its derivatives against the SARS-CoV-2 virus-RBD spike compared to the HCQ drug was carried out using Autodock VINA software. The results explained that artemisinin and its derivatives are more effective when compared to the HCQ drug, which has a Vina score of -5.5 kcal/mol (Sehailia and Chemat, 2020).

Baicalin and Scutellarin

Based on a review article by Muchtaridi et al (2020) and Verma et al (2020), it is explained that baicalin is a phytochemical component contained in the *Scutellaria baicalensis* which has an IC_{50} value of ACE2 activity of 2.24 mM. The inhibition of ACE2 by baicalin and scutellarin can prevent the SARS-CoV-2 virus infection process (Yang et al., 2020). A review article by Huang et al (2020) explained that baicalin could inhibit the activity of the SARS-CoV virus at EC_{50} by 12.5 µg/ml. Baicalin effectively inhibits ACE2 (in vitro study) seen from the IC_{50} parameter of 2.24 mM. In a review article by Khare et al (2020), it is also stated that baicalin and scutellarin can inhibit ACE2 as seen from the docking score parameter in the in silico test results.

Berbamine

Berbamine is an alkaloid component that is found in many *Berberis amurensis* plants (Cao et al., 2017). Based on the latest research conducted by Balmeh et al (2020), a molecular docking test process was carried out using Autodock VINA software from 30 phytochemical components against the target protein of the SARS-CoV-2 virus. Phytochemical components that have the potential to inhibit ACE2 activity: berbamine (-12.3 kcal/mol), naringin (-8.6 kcal/mol), and officinatrione (-8.4 kcal/mol). Berbamine is the most effective compound, can penetrate BBB, and is non-carcinogenic with the recommended dose for humans of 0.0064 mmol/kgBW/day

Carbazole, murrayquinnon, and murrayyanine

Carbazole is an alkaloid class compound that can bind to various receptors on viral

enzymes, including HIV, HSV, HCV, HPV, and HCMV (Caruso et al., 2019). A review article by Gupta et al (2020) explained that the carbazole component (-5.11 kcal/mol) had better spike protein inhibition effectiveness than the Murrayquinone-A component (-4.696 kcal/mol), and murrayanine (-4.502 kcal/mol).

Emodin

Emodin (1,3,8-trihydroxy-6-methylanthraquinone) is a phytochemical compound in the antraquinone class. Emodin has many properties such as antiviral, antibacterial, anti-inflammatory, and anticancer (Dellafiora et al., 2020). Based on previous research, it was found that emodin was effective in inhibiting the interaction between the SARS-CoV virus spike protein and the ACE2 receptor (Xian et al., 2020; Fuzimoto and Isidoro, 2020; Mirzaie et al., 2020; Yang et al., 2020; Jahan and Onay, 2020; McKee et al., 2020; Silveira et al., 2020).

Based on the in vitro test results of the *Rheum sp.* and *Polygonum sp*. using the luciferase assay method with extract concentrations of 0, 10, 50, 100, 200, and 400 µM respectively showed that emodin compounds had the effectiveness of inhibiting spike protein interactions with ACE2 in SARS-CoV virus with IC_{50} = 200 µM (Bernarba and Pandiella, 2020). Meanwhile, based on an article review by Muchtaridi et al (2020), it was also explained that the emodin contained in *Rheum officinale* and *Reynoutria multiflora* had effectiveness against ACE2 seen from in vitro test results with IC_{50} parameters of 1-10 µM / mL and 1-10 µM / mL, respectively. Therefore, it is necessary to have further research on the potential test of emodin against the SARS-CoV-2 virus.

Epigallocatechin-gallate (EGCG), Epicatechin gallate (ECG), and 3-Galloylcatechin

Epigallocatechin-gallate (EGCG) is a component of the significant polyphenol class compounds in the *Camellia sinensis* (L.) (Mhatre et al., 2020). Based on the in silico test results, epigallocatechin gallate effectively inhibits the activity of the SARS-CoV-2 virus spike protein from preventing virus entry (Jahan and Onay, 2020). Compound (-)-epicatechin gallate has a high affinity for spike-RBD SARS-CoV-2 virus. Compound (-)-epicatechin gallate can interact with the amino acid residues of Phe486 and Leu455 in spike-RBD (weak interaction). Meanwhile, a strong interaction is formed on the amino acid Arg403 residue. (-)-epicatechin gallate has an LD_{50} value of 2.558 mol/kgBW (rat) so it is relatively safe for consumption (Istifli et al., 2020).

Based on research conducted by Subbaiyan et al. (2020) by conducting molecular docking testing of components of several types of phytochemicals against the SARS-CoV-2 virus spike protein using the iGEMDOCK version 2.1 analysis software, it was found that EGCG was the most effective component (total bond energy = -130.556 kcal/mol) compared to the other components such as: curcumin (total bond energy = -115.198 kcal/mol), ajoene (total bond energy = -74.2819 kcal/mol), allicin (total bond energy = -62.4326 kcal/mol), aloe emedin (total bond energy = -69.2503 kcal/mol), apigenin (total bond energy = -108.614 kcal/mol), chrysophanol (total bond energy = -107.385 kcal/mol), diallyltrisulfide (total bond energy = -53.2872 kcal/mol), ursolic acid (total bond energy = -89.9499 kcal/mol), and zingerone (total bond energy = -102.184 kcal/mol).

Fisetin

Fisetin (3,3', 4', 7-tetrahydroxyflavone) is a flavonoid class compound found in various types of vegetables and fruits with 2-160 µg/g (Khan et al., 2013). Based on research conducted by Pandey et al (2020), it was found that fisetin (-8.5 kcal/mol) is the most effective compared to other components such as pterostilbene (-6.7 kcal/mol), isorhamnetin (-8.3 kcal/mol), genistein (-8.2 kcal/mol), luteolin (-8.2 kcal/mol), apigenin (-7.7 kcal/mol), and HCQ drug (-5.6 kcal/mol). Fisetin can interact with the S1 and S2 domains on the SARS-CoV-2 virus spike protein and potentially inhibits cell entry (Oladele et al., 2020).

Gingerenone and Zingiberene

Based on previous research by Chakotiya and Sharma (2020), the results of the molecular docking test between the ginger bioactive compounds against the spike protein are as follows: gingerenone (-4.21 kcal/mol), zingiberene (-6.23 kcal/mol), zingerone (-5.96 kcal/mol), shoagol (-3.93 kcal/mol), 1-dehydro6gingerdione (-6.02 kcal/mol), and gingerole (-5.16 kcal/mol). From the results of this study, it was explained that the bioactive components of gingerenone and zingiberene were very effective in inhibiting the interaction between spike protein and ACE2 in the cell entry process. Besides being able to inhibit the cell entry process, ginger can also boost the human immune system. Therefore, ginger (*Zingiber officinale*) is highly recommended for COVID-19 therapy (Chakotiya and Sharma, 2020).

Hesperidin and Its Derivatives

Hesperidin (hesperetin 7-routineoside) is a glycoside compound composed of hesperetin (aglycone) and routineose (glycone). Based on the latest research, it was found that the components of the hesperidin compound and several types of citrus flavonoids can bind to the SARS-CoV-2 virus protein. The presence of an aglycone group, hesperetin, causes this compound to be able to bind to the ACE2 receptor (Verma et al., 2020; Yang et al., 2020; Meneguzzo et al., 2020). Hesperidin is potential to inhibit h-ACE2 with a docking score of -8,111 kcal/mol. Hesperidin can form hydrogen bonds in Gln102, Asp350, Asp382, Tyr385, Leu391, Ala484, Lys562 and Asp206, Glu398, Lys562 on ACE2 protein homologs (Gupta et al., 2020). Based on some research literatures, it was explained that naringin, hesperitin, and naringenin compounds can strongly bind RBD-ACE2 receptors. Naringin is a flavonoid class compound found in TCM from *Exocarpium Citri grandis* (Meneguzzo et al., 2020).

Based on in silico research conducted by Basu et al (2020), using the ClusPro Software program, it was found that hesperidin (ΔG = -8.99 kcal/mol) was the most effective component compared to emodin (ΔG = -6.19 kcal/mol), anthraquinone (ΔG = -6.15 kcal/mol), and rhein (ΔG = -8.73 kcal/mol), chrysin (ΔG = -6.87 kcal/mol). In addition, it was also explained that hesperidin was more effective than HCQ (ΔG = -7.82 kcal/mol).

Kaempferol

Kaemferol compounds can be found in *Brassica oleraceavar*. Kaemferol has good oral bioavailability and excellent binding capacity to spike proteins (Wondkum and Mohhamed, 2020). Kaempferol was able to cause TMPRSS2 to downregulate (49.14-79.48%) at concentrations of 5 and 15 µM. TMPRSS2 is a transmembrane serine enzyme that plays a role

in the interaction process between spike protein and ACE2 (Bernarba and Pandiella, 2020). Besides, kaempferol is also able to bind the C-terminal atom in subunit 1 (S1) of the SARS-CoV-2 virus spike protein with a binding energy of -7.4 kcal/mol better than hydroxychloroquine (-5.6 kcal/mol) (Pandey et al., 2020).

Curcumin

Curcumin is a polyphenol compound that is found in many *Curcuma longa* (turmeric) (Babaei et al., 2020). Based on research conducted by Emirik (2020), it was explained that the bioactive compounds of turmeric are effective in inhibiting the activity of SARS-CoV-2 spike protein. Silveira et al (2020) also explained that curcumin could increase ACE2 expression. Curcumin can inhibit the virus entry process by changing the surface of the viral envelope protein structure so that the entry process is blocked (Zahedipour et al., 2020). A review article by Paraiso et al (2020) explained that the polyphenolic compounds from *Curcuma spp*. (curcumin and its derivatives) are effective in inhibiting the spike protein SARS-CoV-2 compared to the drug nafamostat. Curcumin (-7.8 kcal/mol) can also bind h-ACE2 with the type of interaction $\pi \rightarrow \sigma$. A review article by Soni et al (2020) explained that curcumin could bind to the SARS-CoV-2 virus spike protein, especially in subunit 1.

Essential Oils

Essential oils are volatile components from natural ingredients that are lipophilic (Asif et al., 2020). Based on in silico research, the essential oil components contained in the *Ammoides verticillata* plant are known to have effectiveness against ACE2 seen from the docking score: isothymol (-4.4067 kcal/mol), limonene (-4.4067 kcal/mol), *p*-cymene (-4.3630 kcal/mol), and γ-terpinene (-4.2320 kcal/mol). The isothymol component has the best effect than other essential oil components (Abdelli et al., 2020). Besides, according to reserach conducted by Boukhatem and Zerser (2020), it was explained that aromatic plants that can be utilized for COVID-19 therapy because they have inhibitory power against ACE2 activity include: *Lycoris radiate* (EC_{50} = 2.4 ± 0.2 µg/ml), *Artemisia annua* (EC_{50} = 34.5 ± 2.6 µg/ml), *Pyrrosia lingua* (EC_{50} = 43.2 ± 14.1 µg/ml), *Lindera aggregate*, Saikosaponins B2 (EC_{50} = 1.7 ± 0.1 µM/L), *Rheum officinale* (EC_{50} = 1-10 µg/ml), and *Polygonum multiforum* (EC_{50} = 1-10 µg/ml). Kulkarni et al (2020) carried out a molecular docking test by using the Autodock VINA. The results indicate that bioactive compounds such as as anathole (-5.0 kcal/mol), cinnamaldehyde (-4.3 kcal/mol), carvacrol (-5.2 kcal/mol), geraniol (-5.0 kcal/mol), cinnamyl acetate (-5.2 kcal/mol), L-4-terpineol (-5.1 kcal/mol), thymol (-5.4 kcal/mol) and pulegone (-5.4 kcal/mol) are effective in inhibiting the SARS-CoV virus spike protein.

Nicotianamine

Nicotianamine (NA) is a type of non-peptide trimer amino acid that is found in many higher plants (Takada et al., 2019). NA has a vital role in maintaining the body's balance system (homeostasis) by binding to divalent metal ions such as Fe^{2+}, Cu^{2+}, Ni^{2+}, $Mn^{2+,}$ and Zn^{2+} (Bonneau et al., 2016). Based on a review article by Verma et al (2020) and Yang et al (2020), nicotianamine components have the potential to bind ACE2 in the SARS-CoV-2 virus.

Luteolin

Luteolin (3,4,5,7-tetrahydroxy flavone) is a component of the flavonoid class of compounds which are found in leeks, carrots, celery, parsley, broccoli, and chrysanthemums (Imran et al., 2019). Luteolin can bind to the surface of the SARS-CoV virus spike protein (Fuzimoto and Isidoro, 2020; Yang et al., 2020; Singh et al., 2020). Luteolin is effective in inhibiting the SARS-CoV virus spike protein with an EC50 of 10 µM (Paraiso et al., 2020). A review article by Oladele et al (2020) also explained that the luteolin component can interact with the SARS-CoV-2 virus spike protein, especially in the S1 and S2 domains so that it has the potential to inhibit the cell entry process.

Proanthocyanidin

Proanthocyanidin is a type of secondary metabolite composition of the condensed tannin class which is found in many fruits, nuts, flowers and seeds (Rauf et al., 2019). Based on research conducted by Maroli et al (2020) who tested the procyanidin-A component against ACE2 and the SARS-CoV-2 virus spike protein, it was found that the energy of the procyanidin binding to ACE2 and spike protein were respectively: -50.21 ± 6, 3 kcal/mol and 23.06 ± 4.39 kcal/mol. The presence of a bond between procyanidin and the SARS-CoV-2 virus protein can cause changes in the virus structure so that the infection cycle is disrupted. Based on research conducted by Iheagwam and Rotimi (2020), it was found that the proanthocyanidin B1 component had the binding power to spike-RBD (-6.4 kcal/mol); ACE2 (-9.7 kcal/mol).

Quercetin

Quercetin (2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxychromen-4-one) is a flavonoid class compound that is found in many vegetables and fruits (Batiha et al., 2020). Based on research conducted by Pandey et al (2020), it was found that quercetin compounds were effective in binding the SARS-CoV-2 virus spike protein, especially in the subunit 2 (S2) section with a bond energy of -8.5 kcal/mol. The energy of the quercetin bond is better than that of HCQ at -5.6 kcal/mol (Pandey et al., 2020). Quercetin can bind to the spike protein and ACE2 in the SARS-CoV-2 virus (Mrityunjaya et al., 2020). Based on in silico research by Sen et al (2020), the results showed that the quercetin component had bond energy of -5.88 kcal/mol and affinity energy of -6.4 kcal/mol and was more effective than the drug arbidol. Vijayakumar et al (2020) carried out an in silico testing process of flavonoid compounds against the SARS-CoV-2 Spike protein. These studies indicate that the compound quercetin (-7.8 kcal/mol) is the most potent component. Quercetin can bind the residue chains of Gly496, Asn501, Tyr505, and Tyr453 from the SARS-CoV-2 spike protein. Based on the docking score results, this study recommends that quercetin be subjected to further testing both in vitro and in vivo. Kiran et al (2020) carried out a molecular docking testing and the results of this study indicate that quercetin (LF score = -10,227) is the most effective compound when compared to chrysoeriol (LF score = -9.035), luteolin (LF score = -9.228). These three components are useful in binding the SARS-CoV-2 virus spike protein.

Resveratrol

Resveratrol (3,4',5-trihydroxystilbene) is a polyphenol compound in the stilbenoid

group (Shaito et al., 2020). Resveratrol mechanism is prevent the SARS-CoV-2 virus from entering the body's cells is a natural compound in the polyphenol group (Ferreira et al., 2020). Based on research by Pandey et al (2020), the results showed that resveratrol was effective in binding the SARS-CoV-2 virus spike protein, especially in the subunit 2 (S2) section and the effectiveness of the bond energy (-7.9 kcal/mol) was better than HCQ (-5.6 kcal/mol). A review article by Quiles et al (2020) explained that resveratrol at a dose of 50 mg/kgBW can increase ACE2 levels so that it actively competes with SARS-CoV-2 in occupying the receptors. Resveratrol can interact with S1 and S2 domains on the SARS-CoV-2 virus spike protein and has the potential to inhibit cell entry (Oladele et al., 2020).

Saikosaponin

Saikosaponin is one type of bioactive component found in *Bupleurum spp*., *Scrophularia scorodonia,* and *Heteromorpha spp*. (Sinha et al., 2020[b]). Saikosaponin B2 effectively inhibits viral attachment and penetration by interfering with the spike protein activity (Xian et al., 2020). Sinha et al (2020[b]), conducted a molecular docking test of the saikosaponin against the SARS-CoV-2. The results showed that 5 types of saikosaponin were selected with the highest docking score: saikosaponin V (-8.299 kcal/mol); saikosaponin U (-8.429 kcal/mol); saikosaponin C (-7.274 kcal/mol); saikosaponin K (-6.251 kcal/mol); and saikosaponin 1b (-6.195 kcal/mol). Saikosaponin U and V are the most recommended because they have the best effectiveness in the SARS-CoV-2 spike protein.

Terpenes

Based on research conducted by Muhseen et al (2002), showed that terpene compounds such as: NPACT01552, NPACT01557 and glycyrrhizin had bond energies: -11 kcal/mol, - 10.3 kcal/mol, and -9.5 kcal/mol (the three components with the best docking results). The three components are components of the terpenes found in *Trevesia palmata*, *Aralia dasyphylla*, and *Glycyrrizha glabra*. These results explained that the three components could inhibit the spike protein interaction with ACE2.

Theaflavine (TF)

A review article by Mhatre et al (2020) explained that theaflavins (TF) and theaflavine-3 (TF3) were effective in inhibiting the interaction between the SARS-CoV-2 virus spike protein and the ACE2 receptor seen from the results of a literature review in an in silico study. Theaflavins (TF) has hydrophobic interactions and binds to the residues of Arg454, Phe456, Asn460, Cys480, Gln493, Asn501, and Val503 with ΔG values of -8.53 kcal/mol.

Bioactive Components in The Asparagus Racemosus Plant

Based on research by Chikhale et al (2020[b]), the molecular docking test was carried out to see the interaction between the phytochemical components of the *Asparagus racemosus (Willd.)* Plant against the SARS-CoV-2 virus spike protein. The results showed that the components of Asparoside-C (-7.165 kcal/mol), Asparoside-D (-6.445 kcal/mol), and Asparoside-F (-6.615 kcal/mol) were the most effective in inhibiting RBD protein spikes seen from the lowest docking score.

Bioactive Components in *Solanum tuberosum* and *Brassica Juncea* Plants

Based on research conducted by Dave et al (2020), by testing the interaction between the phytochemical components contained in the *Solanum tuberosum* and *Brassica juncea* plants in silico. The results was found that only three phytochemical components had the potential to bind the SARS virus spike protein: curcumenol (ΔG = -6.43 kcal/mol), N-desmethylselegiline (ΔG = -6.28 kcal/mol), and phentermine (ΔG = -6.25 kcal/mol).

Bioactive Components in *Cinnamomum sp.*

In silico test results of the cinnamon component against the SARS-CoV-2 virus spike protein found that the Pavetannin C1 component (-11.1 kcal/mol) has the potential to inhibit spike protein (Prasanth et al., 2020).

Bioactive Components *in Clerodendrum sp.*

Based on the research conducted by Kar et al (2020), showed that the taraxerol (RBD-spike = -45.19 kcal/mol;) is the most potent when compared to the friedelin (RBD-spike = -42.22 kcal/mol) and stigmasterol (RBD-spike = -41.25 kcal/mol).

Bioactive Components in The *Glycyrrhiza glabra* Plant

The molecular docking test was carried out by Sinha et al., 2020[a] to see any interactions between the bioactive components against the target protein. The results showed that glycyrrhizic acid is the best component in inhibiting the SARS-CoV-2 virus spike protein (Sinha et al., 2020[a]). Based on research conducted by Vardhan and Sahoo (2020), molecular docking results: maslinic acid (-9.3 kcal/mol), glycyrrhizic acid (-9.3 kcal/mol), corosolic acid (-9.4 kcal/mol), 2-hydroxyseneganolide (-9.2 kcal/mol), and oleanane (-9.0 kcal/mol) are useful in binding the SARS-CoV-2 virus spike protein.

Bioactive Components from *Ipomoea obscura* (L.)

The docking test results of the phytochemical components of the *Ipomoea obscura (L.)* showed that the deoxycholic acid was very effective in inhibiting ACE2 (Poochi et al., 2020).

Bioactive Components from *Nigella sativa* L.

Based on research, it was explained that phytochemical components such as nigellidine have a high affinity for the SARS-CoV-2 virus spike protein. Meanwhile, phytochemical components such as Hederagenin, Thymoquinone (essential oil), thymohydro-quinone have a high affinity for ACE2 (Koshak and Koshak, 2020).

Bioactive Components from *Uncaria tomentosa* (cat's claw)

Based on the research conducted by Perez et al (2020), the best docking results from these study: proanthocyanidin C1 (-8.6 kcal/mol), QAG-2 (-8.2 kcal / mol), 3-isodihydrocadambine (-7.6 kcal / mol), uncarine F (-7.1 kcal / mol), and uncaric acid (-7.0 kcal / mol). In this study, it can be explained that the components of proanthocyanidin C1 are the most effective (Perez et al., 2020).

Bioactive Components from *Withania somnifera*

A research by Chikhale et al (2020[a]), the results showed that the phytochemical components: QGRG (-9.25 kcal/mol), withanoside X (-7.07 kcal/mol), ashwagandanolide (-

6.50 kcal/mol), dihydrowithaferin A (-2.82 kcal/mol), and withanolide N (-0.57 kcal/mol) have the potential to inhibit the SARS-CoV-2 virus spike protein. Based on a review article by Straughn and Kakar (2020), information was also presented that withaferin-A (WFA) is a lactone steroid class compound which is very useful in inhibiting the interaction between spike protein and ACE2.

Nutraceuticals

Bioactive Components in Fungi

Ganoderma lucidum is a type of fungus widely used in the TCM treatment system and is commonly known as Ling Zhi (Teekachunhatean et al., 2012). Based on an article review by Chinsembu (2020), it was explained that one type of fungus (*Basidiomycetes*) that has the potential to inhibit spike protein interactions with ACE2 is *Ganoderma lucidum (Curtis) Karst.* These fungi contain bioactive components in the form of *ganoderic acid F* (triterpene compound) with an IC_{50} of 4.7×10^{-6} M.

Lectin

Lectin can inhibit interactions with the ACE2 receptor. Lectins are found in many plants: (1) *Allium porrum L.*, *Urtica dioca L.* and *Nicotiana tabacum L.* (Chinsembu, 2020).

Brown algae

Brown algae (*Ecklonia cava*) contains phlorotannins, which are useful for inhibiting the SARS-CoV virus spike protein and isolates from these algae have received distribution authorization from the FDA (Chinsembu, 2020).

Nisin

Nisin is a food preservative product obtained from lactic acid in bacteria. Based on the research conducted by Bhattacharrya et al (2020), the values of ΔG nisin Z (-10.8 kcal/mol) and nisin H (-11.3 kcal/mol) were higher than those of RBD (-11 kcal/mol). Nisin H is more hydrophilic than nisin Z. Nisin Z and nisin H are very potent in interacting with h-ACE2. Nisin H competitively occupies the ACE2 receptor.

Lactoferrin

Lactoferrin can reduce IL-6, TNF-α, and ferritin. It is also useful in inhibiting the viral entry and replication process (Mrityunjaya et al., 2020).

Zinc Supplement

Zinc supplement (100 µM) can decrease hACE2 activity in rat lungs. The recommended dosage for zinc supplements is 20-92 mg/week (Mrityunjaya et al., 2020).

Teicoplanin

Based on a review article by Wang et al (2020), teicoplanin is a natural compound in the lipoglycopeptide antibiotic class isolated from the fermentation of *Actinoplanes teichomycetius*. Teicoplanin has the effect of inhibiting the virus entry process in binding to the SARS-CoV-2 spike protein on HEK293T and Huh7 cells (IC_{50} = 1.66 µM). HEK293T and Huh7 are cell types that can express ACE2.

Tuna Peptides

A research conducted by Yu et al (2020) focuses on in silico testing of natural peptide

components contained in tuna against ACE2 enzymes in the life cycle of the SARS-CoV-2 virus. The results of molecular docking show that only one peptide can bind ACE2, namely EEAGGATAAQIEM (CDOCKER value = 144 kcal/mol). EEAGGATAAQIEM peptide can inhibit the viral attachment process by forming six hydrogen bonds and six carbon bonds on ACE2 protein residues and changing the charge by electrostatic interactions.

Propolis

A review article by Berretta et al (2020) explained that bioactive components contained in propolis such as myricetin, caffeic acid phenethyl ether, hesperetin and pinocembrin were useful in binding ACE2 seen from the docking score. Based on the in silico test results, it was found that propolis has a% inhibitory activity against ACE2 by 90% with a strong bond. The best% inhibition of ACE2 was found in catechins and p-coumaric acid.

Conclusion

The utilization of nutraceutical agents can be used for COVID-19 therapy as seen from the in silico test results. Phytochemical components such as curcumin, emodin, quercetin, hesperidin, resveratrol, andrographolide, epigallocatechin-gallate and so on can inhibit the interaction between the SARS-CoV-2 virus spike protein and the ACE2 receptor based on the in silico test results. Other components such as nisin, peptides from tuna, propolis, and so on can also be used to inhibit the interaction between the SARS-CoV-2 virus spike protein and the ACE2 receptor. In silico testing is still hypothetical and further research is needed. It is recommended that further research be carried out both in vitro (% ACE inhibition) and in vivo (pre-clinical, clinical, and toxicity) to reassure the effectiveness of the use of nutraceutical agents in the treatment of COVID-19. Nutraceutical agent components need to be developed into pharmaceutical products that are useful for the therapy of COVID-19.

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