Systematic Review: Potential of Curcumin Compounds as Immunostimulants in the Prevention of SARS-CoV 2 Virus

Burhan Ma'arif*, Suryanto, Arianti Lestari, Asna Defi Batrisyia

Department of Pharmacy, Faculty of Health and Medicine, Maulana Malik Ibrahim State Islamic University of Malang, Malang, Indonesia

Email: burhan.maarif@farmasi.uin-malang.ac.id

Abstract

Curcumin is a compound from the turmeric rhizome plant (Curcuma longa) which has immunostimulating activity. This activity has been tested pre-clinically in vitro, in vivo, and in silico so that it has the potential to be used as raw material for drugs in the development of new drugs to prevent the SARS-CoV 2 virus. The purpose of this study was to examine the immunostimulatory activity of turmeric in vitro, in vivo, and in silico and to explore the mechanism of curcumin compounds as immunostimulants. The method used in this systematic review is Systematic-Meta Analysis by identifying articles from several journal databases (GoogleScholar, ResearchGate, ScienceDirect, Garuda Dikti). Furthermore, the article selection process used a guideline prism flow chart. From this process, it was found 15 articles as the main reference, 5 articles containing in vitro research, 5 articles in vivo, and 5 articles in silico from the turmeric rhizome plant. In vitro preclinical tests show that curcumin compounds have an immunostimulating effect which is characterized by the occurrence of proliferation and activation in several types of immune system cells. In vivo study was proven by an increase in phagocytic activity and an increase in leukocyte production in experimental animals. Whereas in silico was proven by the binding of various SARS-CoV 2 receptors.

Keywords: *Curcumin, Curcuma longa, Immunostimulant, Pre-clinical test, COVID-19*

Introduction

The SARS-CoV 2 infection or what we often call COVID-19 is an epidemic that has been worldwide since December 2019 where the first case was reported in Wuhan, China. The SARS-CoV 2 virus causes acute respiratory infections, where this virus belongs to the Coronaviridae family along with the SARS-CoV and MERS-CoV viruses (Gil, 2020). Based on BNPB data, as of April 25, 2021, Indonesia had 1,641,194 positive cases, 1,496,126 patients recovered and 44,594 people died. The incubation period of the SARS-CoV 2 virus is estimated to be around 2-14 days, the virus is transmitted through droplets when coughing and sneezing from person to person. So that this condition can cause symptoms such as cough, fever to shortness of breath which is exacerbated by symptoms of hyposmia, anosmia, and dysgeusia. (Tsatsakis *et al*., 2020).

Coronavirus or SARS-CoV 2 is a virus that has a spiked structure and is composed of glycoproteins. The SARS-CoV 2 virus can pass through mucous membranes, especially the nasal

and laryngeal mucosa, then enter the lungs through the respiratory tract and then to the target organs. This virus infects its host in three stages, the first stage is the virus infects its host by attaching glycoproteins to target cells to form S-glycoprotein with the help of angiotensin-2 (ACE2), transmembrane protease serine-2 (TMPRSS2). The next stage is the stage of replication with RNA that depends on RNA polymerase (RdRp) so that the virus can make new copies of RNA. The next stage is the maturation stage of viral replication in host cells using proteases such as 3C protease and PL-pro. So that this virus can cause leukocyte and lymphocyte levels to still decrease, then the virus spreads through the bloodstream, especially to organs that express ACE2, causing tightness, decreased lymphocytes, and worsening of lesions in the lungs. If this phase is not resolved, Respiratory Distress Syndrome (ARSD), sepsis, and other complications can occur (Laksmiani *et al*., 2020).

Indonesia is a country with a large tropical rainforest area and rich in biodiversity, including medicinal plants. Various studies have been conducted to identify compounds from plants that can be used for treatment. One of the efficacious plants is turmeric (Curcuma longa) which has been used for generations as an immunostimulant, antifungal, anticarcinogenic, antioxidant, antimutagenic, anti-inflammatory, antidiuretic, antidiabetic, gastritis, and some digestive tract disorders. In addition, this plant is also often used to treat flu, cough, fever, smallpox, nosebleeds, and can increase appetite. (Rahman *et al*., 2017; Sengupta *et al*., 2011; Subositi & Wahyono, 2019). The content of this plant is curcumin as a marker compound (Priyadarsini, 2014). Curcumin is a yellow compound from the roots of C. longa. This compound has little activity in the body due to metabolism. Therefore, this compound is more potent, stable, safe, effective, and has better activity (Sundari, 2016).

Many pre-clinical studies have been carried out in vitro, in vivo, and in silico related to its activity as an immunostimulant in the prevention of the SARS-CoV 2. In vitro pre-clinical studies have shown that curcumin can suppress the proliferation of human peripheral blood mononuclear cells (PBMCs), inhibits the expression of IL-2 and NF-kb (Sengupta *et al*., 2011). In vivo activity showed an increase in the production of macrophage cells from TNF-α that occurred due to the effect on the COX-2 (cyclooxygenase-2) enzyme by curcumin resulting in the synthesis of nitric oxide and biomarkers of the inflammatory response. (Arisonya *et al*., 2014; Behera *et al*., 2011). Then in an in silico study, curcumin compounds showed immunostimulatory activity with an increase between the SARS-CoV 2 virus receptor causing hydrogen bonds and hydrophobic interactions that gave rise to good affinity. (Mulatsari *et al*., 2020). Therefore, the purpose of this systematic review was to examine the immunostimulant activity of turmeric rhizome in vitro, in vivo, and in silico and to explore the mechanism of curcumin compounds as immunostimulants. So that it can be used as a contribution to the rationale and scientific information in the development of new drugs for the prevention of the SARS-CoV 2.

Materials and Methods

This systematic review was carried out using the Systematic-Meta Analysis (PRISMA) method (Selcuk, 2019; Snyder, 2019; Gurevitch et al., 2018):

Article Selection Criteria

The inclusion criteria used in compiling this article include: (i). The study refers to the type of pre-clinical test research of the turmeric rhizome curcumin compound which examines the immunostimulant activity, (ii). The study refers to the SARS-CoV 2 virus, (iii). Studies reporting immunostimulating activity for the prevention of the SARS-CoV 2 virus.

The exclusion criteria in compiling this article include: (i). Articles in publication languages other than English and Indonesian, (ii). Research articles published before 2011, (iii). The research article is not in full-text.

Article Search and Selection Strategy

The search for research articles was carried out by identifying articles from several journal databases (GoogleScholar, ResearchGate, ScienceDirect, Garuda Dikti) in April 2021. The article selection process was carried out using a prism flow chart guideline, namely the identification stage by entering keywords *Curcuma longa*, curcurmin, immunostimulants, SARS-CoV 2, and pre-clinical trials on that *database*. The screening stage is done by removing duplicates, titles, and abstracts from research articles that have been obtained from the previous stage. Furthermore, the feasibility study stage is carried out from all research articles obtained from the research inclusion criteria that have been determined. Primary articles were obtained which were used as the targets of linguistic analysis. Then the articles that are considered relevant are included as supporting analyses in this systematic review.

Data analysis

Data collection from each research article was analyzed using the *Systematic-Meta Analysis* method. This method is a quantitative analysis study of various scientific research results that have been published to obtain conclusions according to the objectives of this systematic review.

Results and Discussion

Article Selection

The literature review study was conducted by sorting out the database of research articles as described in **Figure 1**. A total of 91 research articles were obtained from database searches including research articles from GoogleScholar, ResearchGate, ScienceDirect, and Garuda Dikti. After identifying the title, abstract, and discussion of research articles that are relevant to the research, 15 research articles have met the inclusion criteria and 77 research articles have met the exclusion criteria. Thus, 15 research articles were obtained as primary discussions which were included in this systematic review.

Research Criteria

The main criteria of research articles included in the systematic discussion of this review are summarized and analyzed in **Tables 1, 2,** and **3** of a total of 15 research articles or primary data analyzed. There are 5 research articles with an *in vitro* research model, 5 research articles with an *in vivo* research model, and 5 research articles with an *in silico* research model from the turmeric (*C. longa*) rhizome plant which has the potential as an immunostimulant.

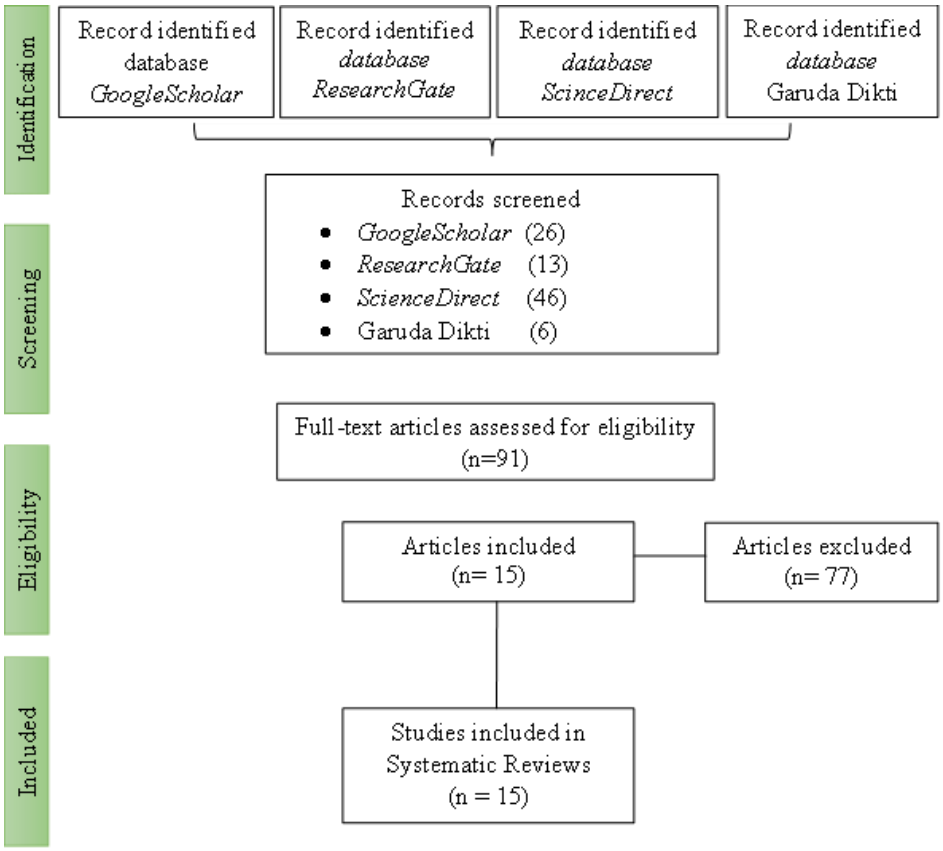

Figure 1. Prisma Guideline Analysis

Results of *in vitro* study analysis

Table 1. Table of *in vitro studies of* curcumin immunostimulant activity

No	Ingredient	Activity	Work mechanism	References
1.	Turmeric (*C. longa*) rhizome curcumin extract	Immunostimulatory activity on human neutrophil cells at a dose of 50 M	– Inhibits *formyl-Methionyl-Leucyl-Phenylalanine* (fMLP) or suppression of *lipopolysaccharide* (LPS) on human neutrophil apoptosis. – Inhibits LPS-induced NF-κB activation – Regulates LPS-induced production of cytokines including MIP-1α, MIP-1β, *IL*- 6, *IL*- 8 (CXCL-8), and GRO-α.	(Antoine *et al.*, 2013)

2.	Turmeric (*C. longa*) rhizome water extract	Immunostimulatory activity on human peripheral blood mononuclear cells (PBMC) with concentrations of 400 and 800 pg/mL	- Regulates the production of pro-inflammatory cytokines, such as TNF-α, *IL*- 6, *IL*- 2, *IL*- 10, and *IL*- 12 significantly.	(Li *et al*., 2018)
3.	Turmeric (*C. longa*) rhizome curcumin extract	Immunostimulatory activity on BHK-21, and Vero-E6 with 5 M. administration	- Inhibits the production of NF-κB - Affects host cells to prevent infection caused by viruses by modulating viral RNA	(Mounce *et al*., 2017)
4.	Turmeric (*C. longa*) rhizome water extract	Immunostimulatory activity in rat splenocytes and mouse macrophages not stimulated by LPS.	- Activation of macrophages that secrete PGE2, *IL*- 6, *IL*- 12 and TNF alpha. - Splenocyte proliferation by lowering PGE2 and *IL*- 12 levels in LPS-stimulated mouse splenocytes - Regulates cytokine release.	(Chandrasekaran *et al*., 2013)
5.	Turmeric (*C. longa*) rhizome curcumin extract	Immunostimulatory activity on macrophages derived from the tip of the kidney and peripheral blood mononuclear cells (PBMC), which has been incubated with curcumin concentration of 50 ug	- Increased levels of Nitric Oxide (NO) in macrophages.	(Elgendy *et al*., 2016)

In vitro, curcumin is believed to have immunostimulating activity as evidenced by its action in modulating the growth and cellular responses of various types of immune system cells. Many studies have proven that curcumin can modulate T cell proliferation and activation, suppress PHA-induced proliferation of *peripheral blood mononuclear cells* (PBMC) and inhibit the expression of *IL*- 2 and NF-B (Sengupta *et al*., 2011). The results of research by Antonie *et al* (2013) showed that curcumin extract of turmeric rhizome (*C. longa*) had immunostimulant activity on human neutrophil cells with the use of a dose of 50 M. Curcumin acts by inhibiting *formyl-Methionyl-Leucyl-Phenylalanine* (fMLP) or suppression of *lipopolysaccharide* (LPS) on human neutrophil apoptosis, inhibiting LPS-induced NF-B activation and regulating LPS-induced cytokine production including MIP-1α, MIP-1β, *IL*-6, *IL*-8 (CXCL-8) and GRO-α.

Research by Li *et al* (2018), showed that the aqueous extract of turmeric rhizome (*C. longa*) has immunostimulant activity on human blood cells, namely *peripheral blood mononuclear cells* (PBMC) with concentrations of 400 and 800 pg/mL. Curcumin can significantly affect the production of pro-inflammatory cytokines, such as TNF-α, *IL*-6, *IL*-2, *IL*-10 and *IL*-12. Another study, according to Mounce *et al* (2017), proved that turmeric (*C. longa*) rhizome curcumin extract had immunostimulant activity at BHK-21, and Vero-E6 with 5 M administration. Curcumin can inhibit the production of NF-κB and the effect on the host cell to prevent the occurrence of an infection caused by a virus with RNA modulate virus.

Research by Chinampudur *et al* (2013), proved that the aqueous extract of turmeric rhizome (*C. longa*) had immunostimulating activity in rat splenocytes and rat macrophages that were not stimulated by LPS. Curcumin acts by activating macrophages that secrete PGE2, *IL*- 6, *IL*- 12 and TNF alpha, proliferating splenocytes by decreasing PGE2 and *IL*- 12 levels in LPS-stimulated mouse splenocytes and also regulating cytokine release.

Research elgendy *et al* (2017), proved that curcumin extract of turmeric (*C. longa*) has immunostimulatory activity on macrophages derived from the tip of the kidney and peripheral blood mononuclear cells (PBMC), which has been incubated with curcumin concentration of 50 ug. Its activities are increased levels of Nitric Oxide (NO) in macrophages. Nitric Oxide (NO) plays an important role in the body's defense mechanisms. NO is believed to be a strong free oxygen radical and engaged in the broad spectrum of diseases which serves as a cytotoxic agent in the pathological process. NO can also inhibit and even kill a wide range of pathogens that enter the body including bacteria, viruses, parasites and fungi.

In vivo Study Analysis Results

Table 2. Table of *In vivo* Studies of Curcumin Immunostimulant Activity

No	Ingredient	Activity	Work mechanism	References
1.	Nanocurcumin PLGA (*Poly D, L-lactic-co-glycolic acid*)	Immunostimulatory activity in albino rats at a dose of 10 mg/kg.	- Increases secondary humoral antibody levels. - Increases the activation of B-lymphocytes, IgM, and IgG. - Increases the production of white blood cells and lymphoid organs.	(Afolayan *et al*., 2018)

			- Modulates the adaptive immune response mediated in mouse cells through decreased DTH (Delayed-Type Hypersensitivity) reactions.	
2.	Turmeric (*Curcuma longa*) rhizome water extract	Immunostimulatory activity in male BALB/c mice with a dose of 200 mg/kg.	- Boost the immune system through the stimulation of T cells	(Li *et al*., 2018)
3.	96% ethanol extract of turmeric (*Curcuma longa*) rhizome	Immunostimulatory activity in laying hens infected with *Salmonella pullorum* by administration of 60% turmeric extract.	- Increase phagocytic activity against foreign proteins that enter the body through the lungs or gastrointestinal tract, as well as toxins produced by bacteria. - Increased number of eosinophils and basophils.	(Hidayah *et al*., 2020)
4.	A mixture of turmeric (*Curcuma longa*) water extract and fish pellet feed	Immunostimulatory activity in pomfret (*Colosoma macropomum*) with a dose of 15 g turmeric/kg feed	- Activate the lymph organs and kidneys to increase the production of leukocytes with a total leukocyte count of 18.6×10^4 cells/mm^3.	(Manurung & Mose N, 2019)
5.	A mixture of turmeric rhizome extract powder and fish pellet feed.	Immunostimulant activity in tilapia (*Oreochromis niloticus*) with 1% curcumin content	- Increases the percentage of activity as well as the phagocytic index significantly.	(Diab *et al*., 2014)

In addition to *in vitro* studies, *in vivo* studies were also conducted to confirm the immunostimulant effect of curcumin compounds in turmeric (*Curcuma longa*) rhizomes. Research conducted by Afolayan *et al* (2018), showed that administration of PLGA (Poly D, L-lactic-co-glycolic acid) nanocurcumin in albino rats at a dose of 10 mg/kg could increase levels of secondary humoral antibodies to stimulate the immune system. there is increased activation of B-lymphocytes and other antibody-secreting cells to become memory cells for sheep red blood cell antigens (SRBCs). In addition to increasing the activation of B lymphocytes by nano curcumin, there is also the possibility of an increase in IgM, IgG, a number of lymphoid organs, and white

blood cell production which confirms that curcumin compounds have potential as immunostimulants. Curcumin compounds can also modulate the adaptive immune response mediated in mouse cells by decreasing the DTH (Delayed-Type Hypersensitivity) reaction after 24 hours.

Another study was conducted on male BALB/c mice with the administration of 200 mg/kg turmeric (*C. longa*) rhizome water extract to increase the immune system through T cell stimulation. Due to this action, the compound curcumin in turmeric (*C. longa)* rhizome extract can exert cytotoxic and anti-metastatic effects in pre-clinical colorectal cancer models (Li *et al*., 2018). The results of Hidayah *et al's* research (2020), stated that in laying hens infected with *Salmonella pullorum* by giving 96% ethanol extract of turmeric rhizome (*C. longa*) at a concentration of 60%, there was an increase in phagocytic activity due to the detoxification function of eosinophils. The detoxification function occurs in foreign proteins that enter the body through the gastrointestinal tract or lungs, as well as toxins produced by bacteria where the number will continue to increase. The presence of an action that increases the number of eosinophils and basophils proves that the curcumin compound in turmeric (*C. longa*) rhizome has an immunostimulant effect.

Based on the results of research by Manurung & Mose N (2019), it was revealed that the administration of a mixture of aqueous extract of turmeric (*Curcuma longa*) and fish pellet feed at a dose of 15 g of turmeric/kg of feed could increase the production of leukocytes in pomfret (*Colosoma macropomum*) with a total leukocyte count of 18, 6 x 104 cells/mm3 for two weeks. This increase in total leukocytes is thought to be due to the curcumin compound activating the spleen and kidney organs in pomfret. The research of Diab *et al* (2014), also supports the effectiveness of curcumin compounds as immunostimulants by proving a significant increase in the phagocytic percentage and phagocytic index of tilapia (*Oreochromis niloticus*) given a mixture of turmeric rhizome extract powder and fish pellet feed with 1% curcumin content. This phagocytic activity has a non-specific primary defense mechanism against the invasion of pathogenic organisms from the host.

Results of *in silico* study analysis

Table 3. Table of *In silico* Study of Immunostimulant Activity of Curcumin Compounds

No	Ingredient	Activity	Work mechanism	References
1.	Curcumin compounds	Has an effective immunostimulant activity because it has a *CHEmPLP* value of -72.9839 at the 1V2I receptor, has a value -20.0148 at 4WEG receptors, value -84.2105 at 2HWI receptors, Value -73.3397 at 3ALP receptors.	- Hydrogen bonds are formed with amino acids ASN-379, THR-533, ARG-158, ARG-386, TYR-415, PRO-120 THR-173 at receptors 1V2I, 2HWI, 4WEG, 3ALP.	(Mulatsari *et al*., 2020)

2.	Curcumin compounds	It has a binding energy value of -8.45 kcal/mol to the PLpro receptor.	- Inhibits PLpro receptor proteases	(Laksmiani *et al*., 2020)
3.	Compounds of curcumin and *cyclocurcumin*	Has a bond energy value of -6.13 and -6.77 kcal/mol to *co-crystallized pyridine* main *protease* receptors -3- *carbinitrile*	- Forms hydrophobic and hydrogen bonds at the *co-crystallized pyridine* -3- *carbinitrile* main protease receptor	(Rajagopal *et al*., 2020)
4.	Curcumin compounds	Has bond energy of -9.08 and -8.07 kcal/mol at the 3CLpro receptor.	- Has hydrogen bonds and hydrophobic bonds at the 3CLpro receptor	(Gupta *et al*., 2020)
5.	Curcumin compounds	Has binding energy of -7.2 kcal/mol at the 6LU7 receptor.	- Forms Van der Waals bonds from amino acid residues PHE140, LEU141, ASN142, SER144, HIS163, HIS164, GLU166, MET49, TYR54, ASP187, ARG188, GLN189.	(Pradani *et al*., 2021)

Based on pre-clinical trials are studying *in silico* compound curcumin in *Curcuma longa* having immunostimulatory activity as evidenced by the case binding with receptors for -72.9839 1V2I than the value *CHemPLP* comparator drugs are zanamivir -67.1235, this drug has a mechanism of action of inhibiting and disturbing the release of the virus on the cell, 1V2I receptor is the receptor hemagglutinin-neuraminidase that are responsible for the formation of the bond between the virus with the host cell. The compound curcumin gives *CHemPLP* bond energy of -20.0148 compared with comparator drugs zanamivir 4WEG -18.4081 receptors. 4WEG receptor is a receptor known as neuraminidase that is responsible for the release of the newly formed virus. Then the compound curcumin provides energy ties with the value *CHemPLP* for -84.2105 compared with the comparator drug ribavirin 2HWI -75.1554 receptors. 2HWI receptor plays a role in the process of viral replication and interaction occurs. The compound curcumin energy forms a bond with a value *CHemPLP* for -73.3397 comparator drugs that have a mechanism docosanol inhibit fusion between the plasma membrane and HSV sheath to prevent the entry of the virus into cells and provide as much as 71.6342 bonds to the receptor 3ALP. 3ALP receptor is the receptor nectin-1 HSV. Compounds that have the value *CHemPLP* best is a compound that has a better selectivity for the receptor. Whereby the negative value of *CHemPLP* the increasingly strong bond between the receptor so that the affinity, the better. (Mulatsari *et al*., 2020).

In the study of Laksmiani *et al* (2020), the compound curcumin has a binding energy value of -8.45 kcal/mol to the PLpro receptor compared to the comparison drug lopinavir with the mechanism of action of inhibiting ACE2 and TMPRSS2 binding of -4.19 at the PLpro receptor (4OWO). The PLpro receptor is a protease that acts on the release process of the N-terminal portion of the polyprotein pp1a/pp1ab. So in this study, curcumin compounds have the ability or

good affinity to bind to the target protein because it has a more negative value than the comparison drug, where the mechanism of action of the curcumin compound inhibits the PLpro protease so that it will interfere with the formation of viruses in host cells.

The curcumin compound in the study of Rajagopal *et al* (2020), *in silico* gave a binding energy value of -6.13 kcal/mol and the cyclocurcumin compound -6.77 kcal/mol compared to the comparison drug hydroxchloroquine which had a score of -5.47 and nelfinavir -5.93 at the main receptor. *co-crystallized pyridine* -3- *carbinitrile protease*. Where a compound can be said to have a good affinity if it has a more negative value, so in this study curcumin compounds have the potential as an immunomodulatory agent with the mechanism of forming hydrogen bonds and hydrophobic interactions on amino acids THR24 and GLN192.

The study of Gupta *et al* (2020), explained that the compound curcumin *in silico* has a binding energy of -9.09 kcal/mol compared to the comparison drug lopinavir, which is -5.4 kcal/mol at the Mpro protein receptor with the mechanism of inhibiting the receptor by binding to form a bond. hydrogen between the amino acids GLU166, Cys141, and His41. So it can be concluded in this study that curcumin compounds have the potential as drug development for SARS-CoV 2 because it has a negative value so that it can be said to have a strong bond.

Then in the study of Pradani et al (2021), *in silico* the curcumin compound provided binding energy of -7.2 kcal/mol but did not differ much from that obtained from the comparison drug, namely -7.7 kcal/mol at the 6LU7 receptor which is a protein receptor of SARS-CoV. 2. Where the *binding affinity* value or energy bond is said to be strong if it gets a more negative value. This means that the compound curcumin has the potential to prevent the SARS-CoV 2 virus by forming a Van der Waals bond PHE140, LEU141, ASN142, SER144, HIS163, HIS164, GLU166, MET49, TYR54, ASP187, ARG188, GLN189.

Conclusion

The immunostimulant activity of turmeric rhizome *in vitro* shows that curcumin compounds have an immunostimulating effect which is characterized by the occurrence of proliferation and activation of several types of *immune system* cells. In *vivo* evidenced by increased phagocytic activity and increased production of leukocytes in experimental animals. While *in silico* evidenced by the binding of various receptors SARS-CoV 2.

Acknowledgement
No one declared

References

Afolayan, F. I. D., Erinwusi, B., & Oyeyemi, O. T. 2018. Immunomodulatory activity of curcumin-entrapped poly d,l-lactic-co-glycolic acid nanoparticles in mice. *Integrative Medicine Research*, *7*(2), 168–175.

Antoine, F., Simard, J. C., & Girard, D. 2013. Curcumin inhibits agent-induced human neutrophil functions in vitro and lipopolysaccharide-induced neutrophilic infiltration in vivo. *International Immunopharmacology*, *17*(4), 1101–1107.

Arisonya, S., Wibisono, G., & Grahita, A. 2014. Efektivitas Ekstrak Kunyit (*Curcuma Domestica*) Terhadap Jumlah Sel Makrofag dan Diameter pada Lesi Ulkus Traumatikus. *Jurnal B-Dent*, *1*(2), 118–125.

Badan Nasional Penanggulangan Bencana. [Online].; 2021 [cited 2021 April 25 Available from: https://bnpb.go.id/.

Behera, T., Swain, P., Sahoo, S. K., Mohapatra, D., & Das, B. K. 2011. Immunostimulatory effects of curcumin in fish, Labeo rohita (H.). *Indian Journal of Natural Products and Resources*, *2*(2), 184–188.

Chandrasekaran, C., Sundarajan, K., Edwin, J., Gururaja, G., Mundkinajeddu, D., & Agarwal, A. 2013. Immune-stimulatory and anti-inflammatory activities of Curcuma longa extract and its polysaccharide fraction. *Pharmacognosy Research*, *5*(2), 71–79.

Diab, A. M., Saker, O. A., Eldakroury, M. F., & Elseify, M. M. 2014. Effects of garlic (Allium sativum) and curcumin (Turmeric, Curcuma longa Linn) on Nile tilapia immunity. *Vet Med J Giza*, *60*(April), C1–C19.

Elgendy, M. Y., Hakim, A. S., Ibrahim, T. B., Soliman, W. S., & Ali, S. E. 2016. Immunomodulatory effects of curcumin on Nile tilapia, Oreochromis niloticus and its antimicrobial properties against vibrio alginolyticus. *Journal of Fisheries and Aquatic Science*, *11*(3), 206–215.

Gil, C., Ginex, T., Maestro, I., Nozal, V., Barrado-Gil, L., Cuesta-Geijo, M. Á., ... & Martinez, A. 2020. COVID-19: Drug Targets and Potential Treatments. *Journal of medicinal chemistry*, 63(21), 12359-12386.

Gupta, S., Singh, A. K., Kushwaha, P. P., Prajapati, K. S., Shuaib, M., Senapati, S., & Kumar, S. 2020. Identification of potential natural inhibitors of SARS-CoV2 main protease by molecular docking and simulation studies. *Journal of Biomolecular Structure and Dynamics*, *1102*.

Gurevitch, J., Koricheva, J., Nakagawa, S., & Stewart, G. 2018. Meta-analysis and the science of research synthesis. *Nature*, *555*(7695), 175–182.

Hidayah, N., Puspita, R., & Mujahidah, M. 2020. Pengaruh Ekstrak Kunyit (Curcuma domestica Val) Terhadap Berat Badan, Jumlah Eosinofil dan Basofil Ayam Petelur yang Diinfeksi Salmonella pullorum. *Jurnal Medik Veteriner*, *3*(2), 230.

Laksmiani, N. P., Febryana Larasanty, L. P., Jaya Santika, A. A. G., Andika Prayoga, P. A., Kharisma Dewi, A. A. I., & Kristiara Dewi, N. P. A. 2020. Active compounds activity from the medicinal plants against SARS-CoV-2 using in silico assay. *Biomedical and Pharmacology Journal*, *13*(2), 873–881.

Li, M., Yue, G. G. L., Tsui, S. K. W., Fung, K. P., & Lau, C. B. S. 2018. Turmeric extract, with absorbable curcumin, has potent anti-metastatic effect in vitro and in vivo. *Phytomedicine*, *46*, 131–141.

Manurung, U. N., & Mose N. 2019. Pemanfaatan kunyit (Curcuma domestica Val) sebagai imunostimulan pada ikan bawal (Colossoma macropomum). *Budidaya Perairan*, *7*(1), 21–25.

Mounce, B. C., Cesaro, T., Carrau, L., Vallet, T., & Vignuzzi, M. 2017. Curcumin inhibits Zika and chikungunya virus infection by inhibiting cell binding. *Antiviral Research*, *142*, 148–157.

Mulatsari, E., Martati, T., Mumpuni, E., & Dewi, N. L. 2020. In Silico Analysis of Antiviral Activity of Analog Curcumin Compounds. *Jurnal Jamu Indonesia*, *5*(3), 114–121.

Pradani, T. C., Manampiring, A. E., Kepel, B. J., Budiarso, F. D., & Bodhi, W. 2021. *Molecular Docking Terhadap Senyawa Kurkumin dan Arturmeron pada Tumbuhan Kunyit (Curcuma Longa Linn.) yang Berpotensi Menghambat Virus Corona*. *9*(2), 208–214.

Priyadarsini, K. I. 2014. The Chemistry of Curcumin: from Extraction to Therapeutic Agent. *Molecules*, 19(12), 20091-20112.

Rahman, D. R., Rimbawan, R., Madanijah, S., & Purwaningsih, S. 2017. Potensi selada air (Nasturtium officinale R. Br) sebagai antioksidan dan agen anti proliferasi terhadap sel MCF-7 secara in vitro. *Jurnal Gizi Dan Pangan*, *12*(3), 217–224.

Rajagopal, K., Varakumar, P., Baliwada, A., & Byran, G. 2020. Activity of Phytochemical Constituents of Curcuma longa and Andropraphis paniculata against coronavirus (COVID-19) an in silico Approach. *Future Journal of Pharmaceutical Sciences*, *6*(104), 1–10.

Selcuk, A. A. 2019. A Guide for Systematic Reviews: PRISMA. *Turkish Archives of Otorhinolaryngology*, *57*(1), 57–58.

Sengupta, M., Sharma, G. D., & Chakraborty, B. 2011. Hepatoprotective and immunomodulatory properties of aqueous extract of Curcuma longa in carbon tetra chloride intoxicated Swiss albino mice. *Asian Pacific Journal of Tropical Biomedicine*, *1*(3), 193–199.

Snyder, H. 2019. Literature review as a research methodology: An overview and guidelines. *Journal of Business Research*, *104*(July), 333–339.

Subositi, D., & Wahyono, S. 2019. Study of the genus curcuma in Indonesia used as traditional herbal medicines. *Biodiversitas*, *20*(5), 1356–1361.

Sundari, R. 2016. Pemanfaatan dan Efisiensi Kurkumin Kunyit (Curcuma domestica) sebagai Indikator Titrasi Asam Basa. *Teknoin*, *22*(8), 595–601.

Tsatsakis, A., Calina, D., Falzone, L., Petrakis, D., Mitrut, R., Siokas, V., Pennisi, M., Lanza, G., Libra, M., Doukas, S. G., Doukas, P. G., Kavali, L., Bukhari, A., Gadiparthi, C., Vageli, D. P., Kofteridis, D. P., Spandidos, D. A., Paoliello, M. M. B., Aschner, M., & Docea, A. O. 2020. SARS-CoV-2 pathophysiology and its clinical implications: An integrative overview of the pharmacotherapeutic management of COVID-19. *Food and Chemical Toxicology*, *146*(September), 111769.