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The Potential of Curcumin in Turmeric (*Curcuma domestica*) and Gingerol in Ginger (*Zingiber officinale*) Combination as Immunity Regulator and Inflammation of SARS-CoV-2 Infection Through Nutrigenomic Approach: A Mini-Review

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Abstract

Background: COVID-19 Pathophysiology caused by SARS-Cov-2 is closely related to immunoregulation and the process of inflammation. Phytonutrients are various types of non-nutritional phyto-compound substances that have biological activity which can be utilized in health maintenance. In the research, as a phytonutrient, these nutrients are closely related to nutrigenomics. Curcumin and gingerol are two types of phytonutrients that have been studied, researched, and developed as a therapy for a disease.

Objective: This research aimed to examine the potential of curcumin and gingerol as immune and inflammation regulators in SARS-CoV-2 infection through a nutrigenomic approach.

Methods: Data that have relevance are collected from several scientific journal databases (Google Schoolar, Elsevier, Science Direct, PubMed, and the Wiley Online Library) published 2010-2021 using different keywords.

Result: Curcumin in turmeric and gingerol in ginger had the potential to be used as a therapy for COVID-19. Curcumin and gingerol can act as primary and secondary antioxidants that can activate endogenous antioxidant enzymes, regulate several cell signaling related to immunity such as Interferon, Nuclear Factor-Kappa Beta, Nitric Oxide, Tumor Necrosis Factor-alpha, as well as stimulation of anti-inflammatory and pro-inflammatory cytokines homeostasis, especially interleukins (IL-1β, IL-6, IL-17, IL-8). In silico, these two compounds have also been shown to have potential as antiviral SARS-CoV-2 by acting as viral protease inhibitors.

Conclusion: The combination of curcumin and gingerol showed synergistic activity in increasing antioxidant and anti-inflammatory capacities. Thus, it had a greater potential to be used as a therapy for COVID-19 in a combination.

Keywords: *SARS-CoV-2, COVID-19, Nutrigenomic, Curcumin, Gingerol.*

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1. INTRODUCTION

coronavirus is a family group of coronaviridae viruses. This virus has been known to infect a variety of hosts (humans and vertebrates). Coronaviruses have emerged in recent years, such as the coronavirus that causes SARS (Severe Acute Respiratory Syndrome), and MERS (Middle Easet Respiratory Syndrome). Until now (2019), the world is faced with SARS-CoV-2 which causes COVID-19 (Corona Virus Disease-19). SARS-CoV-2, like previous strains of the virus, infects the respiratory

tract, and several reports mention it infects the intestines, with various clinical manifestations from acute to chronic. The pathology of this virus is not fully understood, but it is believed that the viral spike protein plays an important factor in the invasion process. This viral infection, plays many roles of the immune system (immunopathogenesis) and inflammation. Uncontrolled immune system (dysregulation) causes excessive inflammation that can cause damage to the multi-related organs. Patients infected with SARS-CoV-2 need good immune system regulation in controlling the severity of the COVID-19 disease. thus, COVID-19 is classified as a self-limiting disease. where the reduction in disease severity and recovery can be controlled by the patient's own immune system as a natural defense modality. but unfortunately, not all individuals have good immunity regulation. so that efforts are needed to control the regulation of immunity and inflammation of patients infected with SARS-CoV-2.

Phytonutrients or phytochemicals are various types of non-nutritional phyto-compound substances that have biological activity (bioactive) which can be utilized in health maintenance. As a phytonutrient, these nutrients are closely related to nutrigenomics. Supplements that are commonly recognized as non-biological several types of phytonutrients that have beneficial bioactivity potential to be used, including polyphenol compounds including flavonoids and their derivatives, anthocyanins, terpenoids, saponins, alkaloids, and steroids. these compounds have been widely reported to have important roles as therapeutic agents of a disease (1,2). Another important thing from phytonutrients is that the existence of a dietary nutritional intake of proportional phytonutrients is proven to help system regulation to create a balance or homeostasis of the immune system which is so needed in patients with immune system dysregulation (3).

Traditional medicine is medicinal ingredients or ingredients derived from plants, animals, minerals, and extract preparations, or mixtures of these ingredients that have been used from generation to generation in the health service system. The use of medicinal plants as alternative medicines in medicine in the community is increasingly widespread. Thus, research is needed so that their use is by the principles of health services, that must be scientifically accountable for their efficacy, safety, and quality standards. The use of plants as traditional medicine has been widely used by people, such as the use of turmeric that is made by herbal medicine and has long been consumed by the community. The curcumin compounds found in turmeric and its family are phytonutrient compounds with a very broad of activities to be used as a therapeutic agent, including antioxidant, anti-inflammatory, anti-rheumatic, immunomodulatory, antiviral, antimicrobial, and hepatoprotective. Plants that are widely used as a traditional medicinal herb besides turmeric are ginger (Zingiber officinale Rosc.). The gingerol content in ginger is proven to have an immunomodulatory, anti-inflammatory, antiviral, antimicrobial, anti-inflammatory, and anti-cancer effect. Therefore, this study will explain the therapeutic potential of curcumin in turmeric and gingerol in ginger in their potential to be used as a COVID-19 therapy which focuses on its effect as an immunity regulator and anti-inflammatory through a nutrigenomic approach.

2. METHODS

In writing this review article, a series of activities were carried out with regard to methods of collecting some library data relevant to the topic, reading and taking notes, then processed as research material. The collection and writing of works is carried out at the Faculty of Pharmacy, Mahasaraswati University Denpasar. This

writing was carried out from February 1, 2021 to February 11, 2021. Data were collected using literature study techniques or literature studies.

The data collected comes from scientific articles, proceedings, books, theses, theses, dissertations, and scientific journals, published from 2010-2021 in Indonesian or English. Information and data that have relevance to the topic are collected from several scientific journal databases such as Google Schoolar, Elsevier, Science Direct, PubMed, and the Wiley Online Library. The keywords written are Curcumin AND Gingerol, Curcumin AND turmeric, Gingerol AND Ginger, Curcumin compound or turmeric as a COVID-19, Gingerol compound or ginger as a COVID-19 therapy, a combination of curcumin AND gingerol, curcumin AND inflammation, Curcumin AND regulating Immune system, Gingerol AND Inflammation, Gingerol AND regulating Immune system, Nutrigenomic curcumin, Nutrigenomic Gingerol.

The data were analyzed by deductive qualitative descriptive technique. Literature that fits the criteria is taken and described and then further reviewed to draw conclusions by comparing literature sources related to the focus of research that departs from general factors to draw specific conclusions.

3. DISCUSSION

3.1 Nutrigenomic Curcumin in Turmeric (*Curcuma domestica*) as a therapy for COVID-19

Turmeric is one of the plants of the spices tribe (Zingiberaceae). The most important part of the use of turmeric is the rhizome. Turmeric leaves are also used for various types of cooking because they can eliminate the rancid smell and add to the aroma of cooking. The curcumin compounds found in turmeric and its family are phytonutrient compounds with a very broad of activities to be used as a therapeutic agent that have very wide activity, including as an antioxidant, antidiabetic, anti-inflammatory, and anti-rheumatic (4,5). Some of the known chemical content of turmeric rhizome is 6% essential oil, consisting of monoterpenes and sesquiterpene compounds, 5% of yellow dye called curcuminoids, protein, phosphor, potassium, iron, and vitamin C. Curcuminoid compounds contain curcumin as the largest component of curcuminoids. Total curcuminoid content is calculated as % of curcumin (6,7). Previous research has proven that the anti-inflammatory test administrating ethanol extract of turmeric to white mice with the dose groups of 100, 250, 500, and 1000 mg/kg BW. The treatment administrated orally is proven in all dose groups to show inhibition of edema formation that occurs in the feet of rats first. It has been injected 1% of carrageenan. The activity referred to as the curcumin modality in turmeric can be used as an anti-inflammatory therapeutic agent by inhibiting prostaglandins and forcing cyclooxygenation. enzyme that causes edema (8,9).

SARS-CoV-2 virus infection is closely related to the Angiotensin Converting Enzyme 2 (ACE2) receptor which is used as the main receptor in its invasion process (10). Curcumin is reported to have activity that can inhibit aminopeptidase N or APN which is an important part of the cellular receptor for alpha CoV. Several types of peptidase have also been reported to be associated with this viral infection, such as APN which is found as alpha CoV receptors, whereas ACE2 as a receptor for SARS-CoV (11). there is a mechanism of action of the CoV virus invasion, where during the process of this virus infection, pathogen-recognition receptors (PRRs) initially have a good sensitivity to the patterns and molecular identities of viral pathogens, so that they will be continued in the activation of cell signaling pathways to produce IFN1 (interferon) type 1) (12). Interferon is one of the major cytokines in the innate immune response that acts as an activator for antiviral

protein proteins to protect uninfected cells. It is known that, the CoV virus can be detected by several types of PRRs, which include Toll-like-receptors (TLRs), a retinoic acid-inducible gene I (RIG-I)-like-receptors, and nucleotide-binding and oligomerization domain (NOD) -like receptors. Occasionally, the SARS-CoV accessory protein has also been known to interfere and damage the PRRs system, and antagonize the interferons response, and avoid the immune response (13–15). The delayed IFNs response can lead to an uncontrolled inflammatory response. It has recently been suggested that VCG Plus may be useful for the regulatory activity of the innate immune response to protect and attack viral invasion by regulating receptor signaling pathways, such as NOD, Toll, and increasing the production of IFNs (16).

From the immune dysregulation caused by this viral disease (SARS, MERS, SARS-CoV-2), it is found that there is a state of overproduction of cytokines by the immune system. this has largely been responsible for the severity and very high mortality rate in infected patients (17,18). There have been many research reports stating that curcumin compounds have anti-inflammatory bioactivity through regulation of NF-κB signaling (19). Curcumin compounds from turmeric, can act as a reducer and stabilizer of oxidation metabolism, which affects the antioxidant repair status and reduction of oxidative stress-causing radical compounds such as ROS (Reactive Oxygen Species) and RNS (Reactive Nitrogen Species) (in vitro) (20). Curcumin has the ability to reduce and stabilize because it can release H atoms. The strong antioxidant property is due to the structure of the chemical compound is formed from 2 methoxylated phenols which are connected in the presence of α and β unsaturated carbonyl groups (21,22).

Research about in silico of curcumin's potential as an antiviral for SARS-CoV-2 was reported by Suravajhala et al (2020). They found that curcumin has a strong binding affinity for nucleocapsid phosphoproteins (PDB ID: 6VYO), membrane glycoproteins (PDB ID: 6M17) along nsp10 (PDB ID: 6W4H). These results indicate that curcumin has high potentiation for use as therapy in COVID-19 patients. As its role in regulating the immune system as well as being anti-inflammatory, curcumin can block important signaling pathways that regulate various proinflammatory cytokine expressions including the Nf-kB and MAPK pathways (23,24). Another study showed that the bioactivity of curcumin has anti-inflammatory and antifibrotic effects mediated by the mechanism of reducing the expression of chemokines and cytokines that play a role in lung infections such as MCP1, IL-6, IL-10, IFN MC (25). In a more specific study on antiviral activity, curcumin is also known to have an inhibitory effect on human respiratory virus (RSV) infections with mechanisms that can inhibit viral replication, TNF release, and the presence of downregulating phospho-NF-κB (26). In the role of a COVID-19 therapy, curcumin can also mediate an anti-edema role. Udem is one of the clinical manifestations of pulmonary inflammation in COVID-19 patients, histopathological examination of several COVID-19 Infected patients have shown clinical manifestations with pulmonary edema, the presence of multi spotted giant cells and fibrinoid material as a result of inflammatory mechanisms (27). Researches are showing that the prophylactic application of curcumin reduces inflammation thereby reducing fluid entry in the lungs of hypoxic rats. It is considered that curcumin can decrease Pro-inflammatory cytokines and the presence of cell adhesion molecules by regulating the activity of NF-κB and also stabilizing HIF1-α (factor 1-alpha) induced hypoxia modeling, which then leads to downregulation of the angiogenic VEGF molecule and is followed by a decrease in pulmonary edema and extravasation of albumin in bronchoalveolar lavage fluid in experimental animals (28,29). Curcumin has

been shown to reduce the production of important inflammatory biomarkers such as interleukins (IL-1β, IL-6, IL-17 and IL-8), TNF-α, MMP (MMP-2, MMP-9) in mice and A549 cells. who are infected with the influenza type A respiration virus (30).

Another report states that curcumin can also reduce the expression of several chemokines such as chemokine ligands (design C-X-C) 1 (CXCL1), CXCL5, and CXCL12 which were found to increase during inflammation of the airway epithelial cells (31). It is believed that, the key to success in reducing the severity and high mortality rate from SARS-CoV infection is very possible by activating the innate immune response to trigger the production of IFN in the early stages of infection. This can also be achieved by administering therapeutic agents that can increase the synthesis of IFN (32). furthermore, it is known that there is also growing evidence about the effect of curcumin administration on IFN activation in several viral diseases (33). Viruses can constantly stimulate the activation of NF-κB and also regulates IFN via interferon regulatory factors which are then produced many antiviral cytokines, activation of antiviral IFN in the JAK / STAT pathway can induce the synthesis of interferon stimulating genes (ISG), the results indirectly stimulating stimulates signaling pathways that are not dependent on IFNs to stop the replication process of the virus (24). Curcumin compounds have been able to effectively suppress the PEDV model of CoV reproduction by stimulating and inducing the in vi vitro activation of interferon-stimulating genes (ISGs), IL-8, and IL-6 from vero cells (34).

3.2 Gingerol Nutrigenomic in Ginger (*Zingiber officinale*) as Therapy for COVID-19

Plants that are widely used as ingredients in traditional medicine besides turmeric are ginger (Zingiber officinale Rosc.). The ginger rhizome contains non-volatile oil, volatile oil components, and starch. The non-evaporating oil called oleoresin is a component that gives a spicy and bitter taste. While the volatile oil called essential oil is a distinctive odor-giving component, a ginger rhizome is a potential source of vitamins (thiamine / B1, C, E) and calcium, iron, magnesium, zinc, sodium, manganese, and phosphorus (35). Fresh ginger contains several chemical ingredients, namely 4-, 6-, 8-, 10-, and 12-gingerol, 6-, 8-, 10- shogaol, flavonoids, phenolics (36,37). Ginger has main compounds such as gingerol, zingeron, and shogaol (6,8,10-gingerol, and 6-shogaol) that are anti-oxidative to scavenge the increasing number of free radicals. under these stress conditions by giving hydrogen atoms (38). The terpenic compounds contained in ginger include β- bisabolane, α-curcumane, zingiberene, α- farnesene, β-sesquipellandri. These compounds were the main components of essential oil which is obtained from ginger rhizome. Apart from the presence of lipid constituents, polysaccharides, organic acids, and raw fiber, it is also found in ginger (39,40). 6-gingerol compound is a bioactive phenolic compound found in the fresh ginger rhizome. 6-gingerol is a promising drug candidate for treating various diseases related to inflammation, cancer, and viral diseases. Fresh ginger has potential as an antiviral against respiratory syncytial virus that attacks humans, this activity is due to the presence of the bioactive phenolic compound Phyto 6-gingerol (41). Previous studies have revealed that shogaol is a product of dried ginger and exhibits higher biological activity including anticancer and antioxidant (42). Therefore, it is very potential to study the possible effects of ginger compounds, especially gingerol, as a therapy for COVID-19.

During the stages and processes of viral infection, various signaling pathways are activated to produce defenses against interferon type 1 (IFN). IFN is a major cytokine that plays a role in providing innate immune responses to activate the release of

antiviral proteins. to protect uninfected cells. In some cases, there was a tendency for the SARS-CoV spike protein to antagonize the IFN response and avoid activation of the immune response. there is a delayed activation of IFN can lead to an uncontrolled inflammatory response (43). There are several research reports that report the effect of IFN activation on SARS-CoV virus replication in vitro. It is known that the antiviral potential of IFN-α, -ß, and -ɣ has been assessed in cell culture, with IFN-ß being the strongest potential inhibitor of the SARS-CoV virus (44). Proinflammatory cytokines (such as IFN-g and TNF-a) simulate the expression and activity of iNOS (inducible nitric oxide synthase) in macrophages cell. Hence, when the production of these cytokines is inhibited, the generation of nitric oxide (NO) is likely to be reduced. It is known that inflammatory mediators (such as NO) play an important role in chronic inflammation, oxidative stress, and fibrosis which affect tissue architecture and impair organ function (45). Several studies have shown that ginger inhibits the expression of genes encoding pro-inflammatory cytokines by various cells. Ginger extract and 6-gingerol can minimize the adverse effects of these parasites on the vital functions of the infected organs through their immunomodulatory effects on the iNOS pathway. Besides, ginger and its main components also have an immunomodulatory effect that does not affect its larvicidal activity (46). Several research reports have proven the potential of ginger and its active components to have potent anti-inflammatory bioactivity. Gingerol ginger has been shown to actively provide protection from inflammatory-related diseases such as ulcerative colitis. The anti-inflammatory effects are mainly related to the regulation of phosphatidyl inositol-3-kinase (PI3K) signaling, protein kinase B (PKB), and NF-κB (39).

6-shagol compound exhibits a protective effect against TNF-α in mice model of chronic intestinal inflammation, preventing upregulation of Claudin-2 and Claudin-1 through inhibition of signaling pathways involved with PI3K / Akt and NF-κB (47). This compound is also reported to be able to inhibit the formation of pro-inflammatory mediators such as PGE2, and NO in animal (mouse) macrophage RAW 264,7 cells (48). The zingeron compound in ginger can inhibit NF-kB activation and reduce IL-1 levels in the colon of inflammatory mice. There is research that states that consuming at a dose of 500 mg of ginger powder routinely can actively prevent an increase in inflammatory markers in the form of cytokines interleukin-1, interleukin-6, and TNF-α (49). 6-gingerol from ginger can decrease H_2O_2 and MDA which are markers of oxidative stress, as well as activating the antioxidant enzyme glutathione in mice (50). Also, ginger and zingerone extracts inhibit the activation of NF-κB and decreased IL-1β levels in rat intestines, which reduced colitis (induced 2, 4, 6-trinitrobenzene sulfonate sulfonic acid) (51). Ginger with gingerol constituents can provide protection against the incidence of enteritis by inducing anti-CD3 antibodies in model mice, and can reduce TNF-α production and activation of Akt. and NF-κB (52). Besides, ginger-derived nanoparticles can prevent inflammation in the intestine by activating several anti-inflammatory cytokines which include IL-10 and IL-22 and can reduce levels of proinflammatory cytokines including TNF-α, IL-6, and IL-1β in experimental mice with models of experiencing acute and chronic colitis (53). Besides, nanoparticles laden with 6-shogaol were found to be shown to reduce the severity of colitis symptoms and provide a repair effect in rat colitis wounds in a sodium dextran sulfate-induced colitis model (54). From various research reports found both in vitro and in vivo have provided evidence that ginger and its bioactive compounds, such as shogaol, gingerol, and oleoresin have potent anti-inflammatory and potent antioxidant bioactivity that is especially important in patients with COVID-

19. Research by Rathinavel et al tried to prove that the 6-gingerol compound from Zingiber officinale can act as a promising drug to treat COVID-19 in silico. The 6-Gingerol compound has very possible drug parameters with excellent ADME pharmacokinetic properties. 6-gingerol proved anti-viral efficiency against SARS CoV-2 by showing the highest binding affinity and interaction with multiple COVID-19 targets including viral proteases, RNA binding proteins, and the Spike protein from the SARS-CoV-2 virus. The results of the DFT research as a study conducted to explain the accuracy of the structural and phytochemical properties of the 6-gingerol compound, prove the reason behind the highest binding affinity between the target protein 6-gingerol and COVID-19. This research proves that 6-gingerol from the ginger plant can be used as a promising drug to treat the novel COVID-19 (55).

Gingerol is also widely reported as a therapy in patients with respiratory-related diseases. Gingerol can induce significant relaxation of human napasa smooth muscle. The compounds 6, 8-gingerol, and 6-shogaol can cause rapid relaxation of the smooth muscle of the pre-contracted airways. The compounds 6, 8-gingerol, and 6-shogaol exerts a relaxing effect on human airway smooth muscle through suppression of 4D phosphodiesterase (56). Gingerol can improve the health status of allergy and asthma patients with a mechanism that can reduce inflammation of the airway and suppress the increase in Th2-mediated immune response in ovalbumin-induced allergic asthma mice (57). It is also known that ginger oil and the bioactive compounds in it, such as citral and eucalyptol, can inhibit rat tracheal contraction due to carbachol in mice models (58). Gingerol also has an active role in treatment of ARDS (acute respiratory distress syndrome) by reducing the duration of mechanical ventilation in patients (59). The results of this paper suggest that ginger and its bioactive properties have a protective effect on some respiratory disorders, by being able to mediate through relaxation-inducing activity of airway smooth muscle and reduction of swelling. Respiratory system disorders are also commonly found in COVID-19 patients. Thus, gingerol and its constituents have great potential for use as a potential therapy in COVID-19 patients.

3.3 Combination of Gingerol in Ginger (*Zingiber officinale*) and Curcumin in Turmeric (*Curcuma domestica*) as Therapy for COVID-19

Combining turmeric and ginger seems to show great potential to produce more potential bioactivity. The combination of ginger and turmeric has been shown to increase the pharmacological activity of the two plants. The results of the anti-free radical activity test using the DPPH method and the FRAP assay, it showed that the combination of ginger and turmeric powder has a higher free radical inhibiting activity from turmeric and ginger powder. Likewise, the total phenolic content reaching 103, 39 ± 0.58 mg / g and total flavonoids reaching 4.27 ± 0.05 mg / 100 g were significantly higher in turmeric ginger powder compared to turmeric powder and ginger powder (60). In the research conducted by Poh *et al* (61) The combination of ginger and turmeric gave free-radical inhibiting activity of 93.64%, while turmeric rhizome only gave free radical inhibitor activity of 69.01% and ginger rhizome was 63.41%. The ability of antioxidants to inhibit the formation of reactive oxygen species (ROS) may underlie its role as an anti-inflammatory. Increased ROS in oxidative stress can trigger the formation of various the pro-inflammatory cytokines TNF-α and IL-6 and their families. the existence of this formation pro-inflammatory cytokines then causes inflammation (62). In testing the potent anti-inflammatory activity of the combination of turmeric and ginger extracts, it was found that this combination gave a The potential anti-inflammatory effects were better than

using single ingredient extracts in inflammation mice induced by carrageenan (63).

The bioactivity of the combination of turmeric and ginger was reported by the research of Ramadan and El-Menshawy (64). They stated that in the pilot test the turmeric-ginger mixture showed a synergistic effect as an anti-inflammatory by reducing edema in arthritis mice. Curcuma domestica (turmeric; rich in phenolic curcuminoids: curcumin, dimethoxy-curcumin, and bisdemethoxycurcumin) and the rhizome of Zingiber officinale (with constituents of gingerol and shogaols) are believed to have synergistic activity with one another. The existence of these preliminary test results was also confirmed by research of Heidari-Beni et al (65) combining turmeric, ginger, and black pepper as therapeutic agents in osteoarthritis patients. They explained that combining ginger and turmeric will mediate a more potent anti-inflammatory activity than its single form, the presence of several active ingredients such as gingerol has a potential ability to regulate PGE in inflammatory processes. Ginger has analgesic and anti-inflammatory effects that inhibit the cyclooxygenase and lipoxygenase signaling pathways and prevent arachidonic acid metabolism (66). Curcumin Curcumin has the potential to provide a protective effect against inflammatory events and damage to the cartilage of the knee (67). Secara lebih rinci, terdapat penelitian yang membuktikan bahwa kurkumin (dosis $\geqslant 3$ μ M) secara signifikan dapat mengurangi IL-1 β dan PGE2 (68). The potentiation of both compounds showed synergistic anti-inflammatory and immunoregulatory activities (65).

The bioactivity of the combination of gingerol and curcumin was also reported by Madkor et al (69). They combined garlic, ginger, and turmeric as an antihyperglycemic and antidislipidemia in diabetic mice. From the results of the research, it was found that the combination of the three extracts of these ingredients had a synergistic effect in increasing insulin production (26-37%) and reducing signs of diabetic metabolic syndrome and cholesterol (80-97%). It increased antioxidant protection system in the range of 31-52% (especially GSH) and significantly reduced lipid peroxidation in the range of 60-97%. The combination of ginger turmeric is believed to be able to increase antioxidant activity, gingerol compounds in ginger and curcumin in turmeric facilitate the activity of endogenous antioxidant enzymes, especially GSH that plays an important role in diseases related to oxidative stress which are found in many metabolic, inflammatory, and infectious diseases (69). In its potential as an antiviral, a combination of gingerol and curcumin compounds is also reported by Patwardhan (70) who states that curcumin (from turmeric), gingerol (from ginger) has anti-inflammatory, immune modulation, and antiviral properties. This was confirmed in his research which resulted that the combination of gingerol, curcumin, and grape extracts had activity as an inactivating agent for the Human noroviruses virus (HNoV) and the hepatitis A virus (HAV). The combination of gingerol and curcumin immune system regulation was reported by Akinyemi et al (71) who investigated the effect of the combination two ingredients in the form of ginger (Zingiber officinale) and turmeric (Curcuma domestica) against the activity of purinergic enzymes and the cholinergic system and levels of inflammatory cytokines in model mice. It was found that this combination of substances was able to show an increase in adenosine and acetylcholine (ACh), which acts as an anti-inflammatory agent with a compensatory mechanism to reduce inflammation and the immune response to the incidence of hypertension, decreased serum butyrylcholinesterase, decreased ATP hydrolysis, acetylcholinesterase, and inhibition of IL-1, IL-6, IFN-γ, and TNF-α), but can increase interleukin-10.

As a combination form for COVID-19 therapy, Oso et al (72) had reported the results of in silico tests on curcumin, gingerol, and allicin compounds. The results showed the potential inhibition of the constituents of curcumin, allicin, and gingerol compounds in cathepsin K components, the main protease of COVID-19, and SARS-CoV 3 C-like proteases using the PyRx-Python Prescription 0.8 program, and free energy of the binding was calculated based on conventional molecular dynamics using LARMD server. The properties of ADMET reveal all of these compounds to have medicinal properties. Curcumin compounds had the highest binding affinity potential with all proteases selected in this study, while allicin compounds had the lowest binding affinity for proteases. In this study, it was also observed that curcumin showed the highest bond-free energy in the range 17.90 ± 0.23, 18.21 ± 0.25, and 9.67 ± 0.08 kcal / mol respectively for the viral component of Cathepsin-K, the main protease for COVID-19. Each of these compounds has activity as an antiviral agent and is expected to have a more potent synergistic effect when combined, especially between gingerol-curcumin (72). Combination of turmeric, ginger, and garlic has high therapeutic potential as an immunostimulant for COVID-19 patients, ginger turmeric antioxidants, and antibiofilm activity, especially from turmeric that is mediated by gingerol and curcumin holds promising bioactivity for the therapy of COVID-19 (73).

4. CONCLUSION

Curcumin in turmeric and gingerol in ginger can potentially be used as a therapy for COVID-19 through their potential as a regulator of immunity and inflammation in SARS-CoV-2 infection researched using a nutrigenomic approach. Curcumin and gingerol can play a role as primary and secondary antioxidants that can activate endogenous antioxidant enzymes, regulate several cell signaling related to immunity such as IFNs, NF-kB, NO, TNF-α, as well as stimulation of anti-inflammatory and pro-inflammatory cytokines homeostasis,. In silico, both compounds have also been shown to have potential as antiviral SARS-CoV-2 by acting as viral protease inhibitors. The combination of curcumin and gingerol shows synergistic activity in increasing antioxidant and anti-inflammatory capacities. Therefore, it has a greater potential to be used as a therapy for COVID-19 in a combination form.

LIST OF ABBREVIATIONS

Ach	: Acetylcholine
ACE2	: Angiotensin-Converting Enzyme 2
ATP	: Adenosine Tri Posphate
COVID-19	: Corona Virus Desease-19
CoVs	: Coronavirus
HIF1-α	: Hypoxia-Induced Factor 1-alpha
HNoV	: Human Noroviruses
HAV	: Hepatitis A Virus
IFNs	: Interferon
IL	: Inter Leukin
ISGs	: Interferon-Stimulating Genes
L-NAME	: L-arginine methyl ester hydrochloride
NF-kB	: Nuclear Factor-Kappa Beta
NO	: Nitric Oxide
NOD	: Nucleotide-binding and Oligomerization Domain
PI3K	: Phoshatidylinositol-3-Kinase
PGE2	: Prostaglandin E2
RIG-I	: Retinoic acid-Inducible Gene I
ROS	: Reactive Oxygen Species
TNF-α	: Tumor Necrossis Factor-alpha

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

No Ethical Approval is needed for this study.

HUMAN AND ANIMAL RIGHT

No Humans and animals were used for this study.

CONSENT FOR PUBLICATION

Not applicable

AVAILABILITY OF DATA AND MATERIALS

Not applicable

FUNDING

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CONFLICT OF INTEREST

The authors stated that there were no conflicts of interest, financial or otherwise, in this research.

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