MINI-REVIEW ARTICLE

The Curcumin and Gingerol Combination as an Immune Regulator and Anti-Inflammatory Agent of SARS-CoV Infection According to a Nutrigenomic Approach: A Mini-Review

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Abstract: ***Introduction*:** The COVID-19 pathophysiology caused by SARS-Cov-2 is closely related to immunoregulation and the process of inflammation. There are therapeutic targets in both, which are ideal for the healing process of infected patients. Phytonutrients are closely related to nutrigenomics. Curcumin and gingerol are two types of phytonutrients that have been studied, researched, and developed as therapeutic agents for diseases.

***Objective*:** This study aimed to examine the potential of curcumin and gingerol as immune regulators and anti-inflammatory agents in SARS-CoV-2 infections using a nutrigenomic approach.

***Methods*:** The literature review method was used in this study. Relevant information was gathered from scientific engines and databases (Google Scholar, Elsevier, Science Direct, Scopus, Wiley Online Library, PubMed) published during 2010-2021, and the data were analyzed by deductive qualitative descriptive technique.

***Results and Discussion*:** Curcumin in turmeric and gingerol in ginger have the potential to be used as a therapy for COVID-19 as they could be immune regulators and anti-inflammatory agents for SARS-CoV-2 infection. Curcumin and gingerol can act as primary and secondary antioxidants that can activate endogenous antioxidant enzymes, regulate cell signaling related to immunity such as interferons, nuclear factor-kappa beta, nitric oxide, and tumor necrosis factor-alpha, as well as stimulate anti-inflammatory and pro-inflammatory cytokine homeostasis, especially interleukins (IL-1β, IL-6, IL-17, IL-8). *In silico*, these two compounds were also proven to have potential as SARS-CoV-2 antivirals by acting as viral protease inhibitors.

***Conclusion*:** The combination of curcumin and gingerol showed synergistic activity with increasing antioxidant and anti-inflammatory capacities. Thus, it has great potential for use in COVID-19 therapy.

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1. INTRODUCTION

Coronavirus (CoV) belongs to a group of the Coronaviridae virus family. It can infect several host species, including humans and other vertebrates. In recent years, new strains of CoV have appeared regularly in various regions around the world, such as CoV acute respiratory syndrome (SARS-CoV) in 2002; these viruses mostly cause respiratory and in-testinal tract infections and induce various clinical manifesta-tions. Although viral pathology is not fully understood, viral proteins and host factors play a key role in the infection process.

Viral infections are well-coordinated and elicit specific responses. In contrast, immune-controlled responses are associated with immunopathogenesis and excessive inflammatory responses, which can result in adverse outcomes such as severe lung damage and multi-organ failure. People infected with CoV must rely on their immune defenses to control the progression of the infection. These diseases are classified as self-limiting diseases. This means that an individual's immune function determines whether they will recover from the infection or whether their initial symptoms will develop into symptoms of other diseases, including severe acute respiratory problems such as pneumonia.

Phytonutrients are bioactive non-nutritional plant compounds that exhibit the capacity to alter biochemical reactions. They affect human health after ingestion. Phytonutrients are closely related to nutrigenomics. Supplements com-

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monly recognized as non-biological nutrients include flavonoids, anthocyanins, carotenoids, polyphenols, triterpenoids, and phytosterols. They have been reported to play important roles in human health as therapeutic agents [1, 2]. It is known that an adequate intake of nutrients and phytonutrients can help regulate immune functions, including increasing defense and resistance to infections while maintaining tolerance [3].

Traditional medicines are made of 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 ser- vice system. The use of medicinal plants as alternative medicines in the community has become increasingly wide- spread. Thus, research is needed to ensure that they adhereto the principles of health services and must be scientifically accountable for their efficacy, safety, and quality standards. Plants have been widely used as traditional medicine. For example, turmeric is used as herbal medicine and has long been consumed by the community. Curcumin, which is found in turmeric, is an isolated compound with a broad range of properties, including antioxidant, anti-inflammato- ry, antirheumatic, immunomodulatory, antiviral, antimicro- bial, and hepatoprotective. Another plant that is widely used as a traditional medicinal herb is ginger (*Zingiber officinale Rosc*.). The gingerol content in ginger has been proven to be immunomodulatory, anti-inflammatory, antiviral, antimicrobial, anti-inflammatory, and anti-cancer agent. This study used a nutrigenomic approach to explain the therapeutic potential of curcumin in turmeric and gingerol in ginger for COVID-19 therapy by investigating their effects as immune regulators and anti-inflammatory agents.

2. METHODS

A series of activities were carried out for this review. Regarding data collection methods, library data relevant to the topic were collected, read, and noted. The findings were used as the research materials. All data were collected by searching the literature.

The data collected were from scientific articles, proceedings, books, dissertations, and scientific journals published between 2020-2021. Information and data relevant to the topic were collected from several scientific journal databases such as Google Scholar, Elsevier, Science Direct, PubMed, and the Wiley Online Library. The keywords searched were curcumin and gingerol, curcumin and turmeric, gingerol and ginger, curcumin compound or turmeric as a COVID-19 therapy, gingerol compound or ginger as a COVID-19 therapy, a combination of curcumin and gingerol, curcumin and inflammation, curcumin and regulation the immune system, gingerol and inflammation, gingerol and regulating the immune system, nutrigenomic curcumin, and nutrigenomic gingerol.

The data were analyzed using a deductive qualitative descriptive technique. Literature that fit the criteria was selected, described, and then further reviewed to conclude. The synthesis process was performed by comparing literature sources related to the scope of the research.

3. DISCUSSION

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

Turmeric is one of the plants of the species tribe *Zingiberaceae*. The most important part of turmeric is the rhizome. Turmeric leaves are also used for cooking because they can eliminate rancid smells and add to the aroma of cooking. Curcumin in turmeric is one of the isolated compounds that have many functions, including antioxidant, antidiabetic, anti-inflammatory, and anti-rheumatic activities [4, 5]. Turmeric rhizome contains 6% essential oil, consisting of monoterpenes and sesquiterpene compounds, 5% yellow dye called curcuminoids, protein, phosphor, potassium, iron, and vitamin C. Curcuminoid compounds contain curcumin as the largest component of curcuminoids. The total curcuminoid content was calculated as the percentage of curcumin [6, 7]. Previous research has proven a successful anti-inflammatory test by administering ethanol extract of turmeric to white mice at doses of 100, 250, 500, and 1000 mg/kg BW. The oral treatment was proven in all doses to show the inhibitionof edema formation in the feet of rats. As much as 1% of carrageenan was injected. The effect of curcumin as one of the active ingredients of turmeric can be seen from its capacity in inhibiting the formation of prostaglandins and suppress- ing the activity of the cyclooxygenase enzyme that causes edema [8, 9].

SARS-coronavirus requires angiotensin-converting enzyme 2 (ACE2) as its main receptor [10]. Curcumin inhibits aminopeptidase N (APN), which has been identified as a cellular receptor for alpha CoV. Several peptidases have been well-described as cellular CoV receptors, including APN as a receptor for alpha CoV, and ACE2 as a receptor for SARS-CoV [11]. During viral infection, host patho- gen-recognition receptors (PRRs) are initially sensitized by molecular patterns associated with viral pathogens, and the cascade of signaling pathways is activated to produce inter- feron type 1 (IFNs) [12]. IFNs are cytokines that stand outin the innate immune response and are considered to in- crease the release of antiviral proteins to protect uninfected cells. CoV can be sensed by three types of PRR, including Toll-like receptors, retinoic acid-inducible gene I-like (RIG- I) receptors, and nucleotide-binding and oligomerization do-main-like (NOD) receptors. Occasionally, SARS-CoV acces-sory proteins can interfere with PRR, antagonize the IFNs re-sponse, and avoid the immune response [13-15]. The de- layed IFNs response can lead to an uncontrolled inflammato-ry response. VCG Plus may be useful in regulating innate im-mune responses to invading viruses by regulating receptor signaling pathways, such as NOD and Toll, and increasing the production of IFNs [16].

From the immune dysregulation caused by these viral diseases (SARS, MERS, SARS-CoV-2), it has been found that there is a state of overproduction of cytokines by the immune system. It is largely responsible for the high mortality rate in patients infected with these viruses [17, 18]. Many kinds of research works have shown that curcumin possess-

es an anti-inflammatory function *via* NF-κB signaling [19]. Curcumin acts as a reducing and stabilizing agent that can improve antioxidant status and reduce reactive oxygen species (ROS) and reactive nitrogen species (RNS) in macrophages (*in vitro*) [20] because it can release H atoms. The strong antioxidant property is due to its chemical structure consisting of two methoxylated phenols connected by α and β of unsaturated carbonyl groups [21, 22].

In silico research on curcumin's potential as an antiviral for SARS-CoV-2 was conducted by Suravajhala *et al.* They found that curcumin had a strong binding affinity for nucleocapsid phosphoproteins (PDB ID: 6VYO), membrane glycoproteins (PDB ID: 6M17), and nsp10 (PDB ID: 6W4H). These results indicated that curcumin had a high potential for COVID-19 therapy. In addition to its role as an immune regulator and anti-inflammatory agent, curcumin can also block important signaling pathways that regulate various proinflammatory cytokine expressions, including the Nf-kB and MAPK pathways [23, 24]. Curcumin exerts anti-inflammatory and antifibrotic effects by reducing the expression of important chemokines and cytokines involved in lung infections, such as IFN MC, MCP-1, IL-6, and IL-10 [25]. Curcumin has an inhibitory effect against human respiratory virus (RSV) infections by preventing RSV replication, releasing TNF-alpha, and downregulating phospho-NF-κB [26]. In 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 patients showed pulmonary edema along with an inflammatory group consisting of fibrinoid materials and multi-spotted giant cells [27]. Research has shown that the prophylactic application of curcumin reduces inflammation, thereby reducing fluid entry in the lungs of hypoxic rats. Curcumin can decrease pro-inflammatory cytokines and cell adhesion molecules by modulating NF-κB activity and stabilizing hypoxia-induced factor 1-alpha (HIF1-α), causing downregulation of angiogenic molecules such as VEGF. This is followed by decreased pulmonary edema and albumin extravasation in rat bronchoalveolar lavage fluid [28, 29]. Curcumin reduces the production of TNF-α, IL-1β, IL-6, IL-17 and IL-8, MMP-2, and MMP-9 in mice and A549 cells infected with the influenza A virus [30].

Curcumin also reduces the expression of chemokinessuch as chemokine ligands (C-X-C design) 1 (CXCL1), CX-CL5, and CXCL12 which increase during inflammation in airway epithelial cells [31]. The key to success in reducing the fatality of SARS-CoV may be the activation of the in- nate immune response to trigger IFN production in the earli-est stages of the disease. This can be achieved through the administration of agents that can enhance IFN synthesis,such as poly ICLC [32]. There is growing evidence of curcu-min's effects on IFN in different viral diseases [33]. Viruses can stimulate NF-κB and interferon regulatory factors to pro-duce many antiviral cytokines. Antiviral IFN *via* the JAK/S-TAT pathway induces the synthesis of various interferon-stimulating genes (ISGs). The results indirectly stimulate IFN-independent pathways to stop various stages of viral replication [24]. Curcumin can suppress the PEDV model of coronavirus reproduction by stimulating interferon-stimulating genes (ISGs) and cytokines (IL8 and IL6) from Vero cells by triggering innate immunity from the host [34].

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

One of the other plants widely used as traditional medicine is 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 ginger its spicy and bitter taste. The volatile oil, called essential oil, is a distinctive odor-giving component. A ginger rhizome is a potential source of thiamine (B1), vitamin C, vitamin E, calcium, iron magnesium, manganese, phosphorus, sodium, and zinc [35]. Fresh ginger contains several chemical ingredients, namely 4-, 6-, 8-, 10-, and 12-gingerol, 6-, 8-, and 10- shogaol, flavonoids, and phenolics [36, 37]. Ginger has main compounds such as gingerol, zingerone, and shogaol (6-gingerol (6G), 8-gingerol (8G), 10-gingerol (10G), and 6-shogaol (6S)). These are anti-oxidative compounds that can be used to scavenge the increasing number of free radicals under stress conditions by introducing hydrogen atoms [38]. The terpenes in ginger include β- bisabolane, α- curcumane, zingiberene, α- farnesene, and β- sesquipellandri. These compounds are the main constituents of ginger essential oil. Additionally, polysaccharides, lipids, organic acids, and raw fiber are 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 antiviral properties against human respiratory syncytial viruses due to the presence of the bioactive phenolic Phyto compound 6-gingerol [41]. Previous studies have revealed that shogaol is a product of dried ginger and exhibits higher biological functions, including anticancer and antioxidant properties [42]. Therefore, the possible ef- fects of ginger compounds, especially gingerol, as COVID-19 therapy is worth studying.

During viral infection, a cascade of signaling pathways is activated to produce interferon type 1 (IFNs). IFNs are cytokines that stand out in the innate immune response and are thought to increase the release of antiviral proteins to protect uninfected cells. Occasionally, SARS-CoV accessory proteins antagonize the IFNs response and evade the immune response. The delayed IFNs response can lead to an uncontrolled inflammatory response [43]. Various research works have reported the effects of IFNs on SARS-CoV replication *in vitro*. The antiviral potential of IFN-α, -ß, and -ɣ has been assessed in cell culture, with IFN-ß being the strongest inhibitor of SARS-CoV [44]. Proinflammatory cytokines (such as IFN-g and TNF-a) simulate the expression and ac- tivity of inducible nitric oxide synthase (iNOS) in macrophages. Hence, when the production of these cy- tokines is inhibited, the generation of nitric oxide (NO) is likely to be reduced. It is known that inflammatory media- tors (such as NO) play an important role in chronic inflam-

mation, 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. In addition, ginger and its main components also have an immunomodulatory effect that does not affect its larvicidal activity [46]. Several studies have shown that ginger and its active constituents have anti-inflammatory properties. They can protect against inflammation-related diseases such as colitis. The anti-inflammatory effect is mainly related to phosphatidyl inositol-3-kinase (PI3K), protein kinase B (Akt), and activated nuclear factor kappa light chain enhancer B cells (NF-κB) [39].

The 6-shagol compound exhibits a protective effect against TNF-α in mice with chronic intestinal inflammation. It can prevent the upregulation of Claudin-2 and Claudin-1 by inhibiting 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 nitric oxide and prostaglandin E2 (PGE2) in mouse macrophage RAW 264,7 cells [48]. The zingerone in ginger can inhibit NF-kB activation and reduce IL-1 levels in the colon of mice experiencing inflammation. A previously conducted research states that consuming 500 mg of ginger powder can prevent the increase in inflammatory cytokines IL-1, IL-6, and TNF-α [49]. In addition to that, 6-gingerol from ginger can decrease H_2O_2 and MDA levels and increase antioxidant enzyme activity and glutathione in mice with oxidative damage caused by chlorpyrifos [50]. Furthermore, ginger and zingerone extracts inhibit the activation of NF-κB and decrease IL-1β levels in rat intestines, which leads to reduced colitis caused by 2, 4, 6-trinitrobenzene sulfonate sulfonic acid [51]. Ginger also protects mice from anti-CD3 antibody-induced enteritis. Additionally, ginger can reduce TNF-α production and activation of Akt and NF-κB [52]. Moreover, ginger-derived nanoparticles can prevent intestinal inflammation by increasing levels of anti-inflammatory cytokines, such as interleukin-10 (IL-10) and IL-22, and reducing levels of proinflammatory cytokines, such as TNF-α, IL-6, and IL- 1β, in rats with acute colitis and chronic colitis [53]. Nanoparticles loaded with 6-shogaol have been found to reduce symptoms and improve wound repair in mice with sodium dextran sulfate-induced colitis [54]. Overall, *in vitro* and *in vivo* research works have shown that ginger and its bioactive compounds, such as 6-shogaol, 6-gingerol, and oleoresin, have strong anti-inflammatory and antioxidant properties that are significant for patients with COVID-19. Research by Rathinavel proved 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 drug parameters with excellent ADME pharmacokinetic properties. The 6-gingerol showed 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 DFT research was conducted to explain the accuracy of the structural and phytochemical properties of the 6-gingerol compound. The results of the study showed that the anti-viral efficiency of the 6-gingerol was due to the highest binding affinity between the target proteinof 6-gingerol and COVID-19. This study proved that 6-gin- gerol from the ginger plant can be used as a promising drug to treat patients with COVID-19 [55].

Gingerol is also widely reported as therapy for patients with respiratory-related diseases. It can induce significant relaxation of the smooth human respiratory muscle. The 6-gingerol, 8-gingerol, and 6-shogaol can cause rapid relaxation of the smooth muscle of the pre-contracted airways. They promote agonist-induced relaxation of the smooth human respiratory muscle *via* 4D phosphodiesterase suppression [56]. Gingerol can improve the health status of allergy and asthma patients by reducing airway inflammation and suppressing Th2-mediated immune responses in ovalbumin-induced allergic asthmatic mice [57]. Furthermore, ginger oil and its bioactive compounds, including citral and eucalyptol, inhibit rat trachea contractions caused by carbachol [58]. Gingerol also has an active role in reducing the duration of mechanical ventilation in patients with acute respiratory distress syndrome (ARDS) [59]. The results of this paper suggested that ginger and its bioactive properties had a protective effect on respiratory disorders. They at least mediate them by inducing relaxation in the smooth muscle of the respiration and attenuation of respiration resistance and inflammation. Respiratory system disorders are also commonly found inCOVID-19 patients. Thus, gingerol and its constituents have great potential as COVID-19 therapy.

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

The combination of turmeric and ginger seems to produce more potential bioactivity. This combination has been shown to increase the pharmacological activity of the two plants. The free radical scavenging activity test was conducted with the DPPH assay and the iron-reducing antioxidant power test (FRAP assay). The results showed that the combination of ginger and turmeric powder had a higher free radical inhibiting activity than turmeric and ginger powder. Likewise, the total phenolic content (103.39 ± 0.58 mg/g) and flavonoids (4.27 ± 0.05 mg/100 g) were significantly higher in combined turmeric ginger powder compared to turmeric powder and ginger powder alone [60]. In a study conducted by Poh *et al.* [61], it was shown that the combination of ginger and turmeric gave free-radical inhibiting activity of 93.64%. The same study showed that turmeric rhizome only gave a free radical inhibitor activity of 69.01%, and ginger rhizome only gave a free radical inhibitor activity of 63.41%. The ability of antioxidants to inhibit the formation of reactive oxygen species (ROS) may underlie its role as an anti-inflammatory agent. Increased ROS in oxidative stress can trigger the formation of various pro-inflammatory cy- tokines such as TNF-α and IL-6. The formation of these pro-inflammatory cytokines then causes inflammation [62]. The

anti-inflammatory activity of a combination of turmeric and ginger extracts has been tested. It was found that this combination gave a better anti-inflammatory effect than using the extract alone in rat's inflammation induced by carrageenan [63].

The bioactivity of the combination of turmeric and ginger was studied by Ramadan and El-Menshawy [64]. They stated that, in the pilot test, the turmeric-ginger mixture showed a synergistic effect as an anti-inflammatory agent by reducing edema in arthritis mice. *Curcuma domestica* (turmeric; rich in phenolic curcuminoids: curcumin, dimethoxy-curcumin, and bisdemethoxycurcumin) and *Zingiber officinale* (ginger; rich in stinging phenolic compounds: gingerols and shogaols) are believed to have synergistic activity with one another. The results of this preliminary test were also supported by the research of Heidar- i-Beni *et al.* [65], which combined and used turmeric, gin- ger, and black pepper as therapeutic agents in osteoarthritis patients. They explained that the combination of ginger and turmeric would mediate a more potent anti-inflammatory property compared to their single forms, as well as the ability of prostaglandins in the inflammatory process. Ginger has analgesic and anti-inflammatory effects for inhibiting the COX2 and LOX pathways and preventing arachidonic acid metabolism [66]. Curcumin has a protective effect against knee inflammation and damage to knee cartilage [67]. In more detail, curcumin (≥3 μM) significantly reduced IL-1β (p <.05) and PGE2 levels (p <.001) [68]. Additionally, plas- ma levels of IL-6, IL-8, and Matrix Metalloproteinase-3were refined. The potential 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 com- bined garlic, ginger, and turmeric to be used as an antihyperglycemic and anti-dyslipidemia in diabetic mice. The results of the research showed that the combination of the extracts had a synergistic effect for increasing insulin production(26-37%) and reducing signs of diabetic metabolic syn- drome and cholesterol (80-97%). It increased the antioxidantdefense system (31-52%, especially GSH) and reduced lipid peroxidation (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. These enzymes play an important role in diseases related to oxidative stress, which is established in many metabolic, inflammatory, and infectious diseases [69]. The combination of gingerol and curcumin compounds as a potential antiviral has also been reported by Patwardhan *et al*. [70]. They stated that curcumin (from turmeric) and gingerol (from ginger) have anti-inflammatory, immune modulation, and antiviral properties. This was confirmed in their research, which showed that the combination of gingerol, curcumin, and grape extracts could inactivate the Human noroviruses virus (HNoV) and the hepatitis A virus (HAV). The combination of gingerol and curcumin for immune system regulation was reported by Akinyemi *et al.* [71]. They investigated the effect of the combination of ginger (Zingiber officinale) and turmeric (Curcuma domestica) on the activity of purinergic enzymes and the cholinergic system, as well as inflammatory cytokine levels in (L-arginine methyl ester hydrochloride (L-NAME)) rats. It was found that the combination of these two ingredients could increase the production of adenosine and acetylcholine (ACh). These are important anti-inflammatory agents with compensatory mechanisms to reduce inflammation and immune response in hypertension, decrease serum butyrylcholinesterase, and decrease ATP hydrolysis, acetylcholinesterase, and inhibition of interleukin-1 and -6, interferon-γ, and tumor necrosis factor-α. However, they can also increase interleukin-10.

As a form of 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 curcumin, allicin, and gingerol against cathepsin K, the main protease of COVID-19. They also showed the potential inhibition of a SARS-CoV 3 C-like protease by using PyRx-Python Prescription 0.8. The free energy of the binding was calculated based on conventional molecular dynamics using the LARMD server. The properties of ADMET revealed all of these compounds to have drug-like properties. Curcumin had the highest binding affinity with all selected proteases, while allicin had the lowest binding affinity to proteases. Furthermore, it was observed that curcumin showed

Table 1. Potential compounds of curcumin, gingerol, and their combination.

Compounds	Activity	Mechanism
Curcumin	Antiviral	Inhibits 3Cl protease Vero E6 cells in SARS-CoV [74].
		Inhibits cathepsin K (*in silico*), which is a major protease component of COVID-19, and a SARS-CoV 3 C-like protease [72].
		Inhibits viral replication at the budding stage against the respiratory syncytial virus [76].
		Inhibits RNA replication and causes downregulation of PGC-1α in hepatitis C and B virus [75].
		Suppresses viral replication in cells by involving proteasome inhibitors in the Dengue-2 virus [76].
	Anti-inflammatory and immunomodulator	Inhibits the expression of NF- κB and TNF- α [77].
		Inhibits major inflammatory interleukins (IL-1β, IL-6, IL-8, IL-10) [78].
		Inhibits the chemokine macrophage inhibitory factor (MIF), macrophage chemoattractant protein [79]
		Inhibits arachidonic acid (prostanoids and leukotrienes) [80]
		Inhibits extracellular TLR (TLR2, TLR4, dan TLR8) and intracellular (TLR9) [30, 81]

Compounds	Activity	Mechanism
Gingerol	Antiviral	Inhibits the invasion of human respiratory syncytial virus (HRSV) by reducing HRSV-induced plaque formation in respiratory mucosal cell lines [41].
		Inhibits main protease (Mpro) 6LU7 (COVID-19) (*in silico*) [82]
		Interacts with viral proteases, RNA binding protein, spike protein SARS CoV-2 (*in silico*) [55]
		Inhibits hepatitis C virus RNA replication [83, 84]
		Destroys protein components of influenza A (H1N1) virus (*in silico*) [85]
		Virucidal against herpes simplex virus types 1 and 2 [86]
	Anti-inflammatory and immunomodulatory	Inhibits NF-B expression and decreases PGE2, IL-6, and IL-8 [90].
		Affects claudin-2 upregulation *via* inhibition of phosphatidylinositol-3-kinase/Akt [39].
		Decreasing the levels of nitrite, PGE2, IL-6, and IL-8 through NF-kB [87].
		Inhibits IKKβ activity for NF-B activation and suppression [88].
		Affects downregulating of COX-2, iNOS [89].
		Increases expression of CD3+CD4+:CD3+CD8+ [90].
		Modulates the expression of IL-12 and TGF-β [91].
		Inhibits RORγt and T-bet gene expression in rheumatoid arthritis [92].
Combination of turmeric and gingerol	Antioxidant	Shows a synergistic effect of increasing SOD and GSH-Px, lowering MDA, increasing the total phenolic content of the combination of turmeric and ginger extracts, possibly mediated by curcumin and gingerol [93, 94].
	Anti-inflammatory	Decreases proinflammatory cytokines (TNF-α, IL-1β, and IL-6) and increases anti-inflammatory cytokines (IL-4 and IL-10) [95].
	Antidiabetic	Shows a synergistic effect in increasing insulin levels and lowering HbA1C [96].
	Antihyperlipidemic	Lowers lipid peroxidation, total cholesterol, LDL, MDA, and increases HDL [69].
	Antirheumatic	Shows a synergistic effect on improving the histopathological profile of the ankle joints, blood leukocytosis, and thrombocytosis, iron deficiency [64].

the highest bond-free energies of 17.90 ± 0.23, 18.21 ± 0.25, and 9.67 ± 0.08 kcal/mol, respectively, for Cathepsin K, the main protease of COVID-19, and a SARS-CoV 3 C-like protease. Each of these compounds showed activity as antiviral agents and are expected to have a more potent synergistic effect when combined, especially gingerol and curcumin. The combination of turmeric, ginger, and garlic has high therapeutic potential as an immunostimulant for COVID-19 patients. A combination of ginger and turmeric shows potential antioxidant and antibiofilm activities, especially turmeric, mediated by gingerol and curcumin. This combination holds promising bioactivity for COVID-19 therapy (Table **1**) [73].

CONCLUSION

Curcumin and gingerol can potentially be used as COVID-19 therapy. This is due to their potential as immune regulators and inflammatory agents of SARS-CoV-2 infection, according to a nutrigenomic approach. Curcumin and gingerol can act as primary and secondary antioxidants that activate endogenous antioxidant enzymes, regulate the signaling of cells related to immunity, such as IFNs, NF-kB, NO, TNF-α, and stimulate anti-inflammatory and pro-inflammatory cytokines' homeostasis. *In silico*, both compounds have also been shown to have potential as antivirals for SARS-CoV-2 by acting as viral protease inhibitors. The combination of curcumin and gingerol showed synergistic activity in increasing antioxidant and anti-inflammatory capacities; therefore, their combination has a greater potential for COVID-19 therapy.

LIST OF ABBREVIATIONS

Ach = Acetylcholine

ACE2 = Angiotensin-Converting Enzyme 2 =

ATP = Adenosine Tri Phosphate

COVID-19 = Corona Virus Disease-19

CoVs = Coronavirus

HIF1-α = Hypoxia-Induced Factor 1-alpha

HNoV = Human Noroviruses

HAV = Hepatitis A Virus

IFNs = Interferon

IL = Interleukin

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 Necrosis Factor alpha

CONSENT FOR PUBLICATION

Not applicable.

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None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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