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(REVIEW ARTICLE)

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Curcumin as anti-inflammatory therapy in Covid-19 cases: A literature review

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Abstract

The rhizome of the Curcuma longa (turmeric rhizome) plant has long been used as traditional medicine. Various studies have found that the active substance curcumin in turmeric rhizome has various effects, such as: anti-inflammatory, antifungal, and anti-bacterial for infectious disease. This review article aims to indicate the potential anti-inflammatory effects of curcumin in the treatment of Covid-19. Articles search were performed on three databases (PubMed, Sage Journals, and Nature Portfolio), in which 97 articles were found and filtered based on title, abstract, year of publication, open access, and full text review to obtain 5 relevant articles. This review explains a large potential anti-inflammatory effect of curcumin for treating Covid-19. After the effects proved for many diseases with inflammatory symptoms, similar results were also found in in-vitro testing and clinical trials on Covid-19 cases.

Keywords: Covid-19; Curcumin; Anti-Inflammatory; Traditional medicine; Infectious disease

1. Introduction

1.1. Covid-19

Corona Virus Disease (Covid-19) is a disease caused by the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) [1]. Transmission of SARS-CoV-2 from symptomatic patients occurs through droplets released when coughing or sneezing. In humans, SARS-CoV-2 primarily infects cells in the airways lining the alveoli. Inside cells, SARS-CoV-2 duplicates genetic material and synthesize the necessary proteins, then forms new virions that appear on the cell surface. Dysregulation of the immune system plays a role in tissue damage in SARS-CoV-2 infection. Inadequate immune response leads to viral replication and tissue damage. On the other hand, excessive immune response can cause tissue damage [2].

COVID-19 patients have a broad clinical manifestation, ranging from asymptomatic, mild symptoms, pneumonia, severe pneumonia, ARDS (Acute Respiratory Distress Syndrome), sepsis, to septic shock. ARDS is the leading cause of death in COVID-19 patients. The cause of ARDS in SARS-CoV-2 infection is a cytokine storm, which is an uncontrolled systemic inflammatory response due to the release of large amounts of proinflammatory cytokines (IFN-α, IFN-γ, IL-1β, IL-2, IL-6, IL-7, IL-10 IL-12, IL-18, IL-33, TNF-α, and TGFβ) and large amounts of chemokines (CCL2, CCL3, CCL5, CXCL8, CXCL9, and CXCL10) [3].

The course of the disease begins with an incubation period of about 3-14 days (median 5 days). At this time leukocytes and lymphocytes are still normal or slightly decreased and the patient is asymptomatic. In the next phase (early

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symptoms), the virus spreads through the bloodstream, presumably mainly in ACE2-expressing tissues such as the lungs, gastrointestinal tract and heart. Symptoms in this phase are generally mild. The second attack occurs four to seven days after the initial symptoms appear. At this time the patient could have fever and began to have shortness of breath. The lesions in the lungs worsened and the lymphocytes decreased. Inflammatory markers begin to increase and hypercoagulability occur. If not resolved, the next phase of inflammation becomes increasingly uncontrolled, a cytokine storm occurs which results in ARDS, sepsis, and other complications [3].

1.2. Inflammation

Inflammation is a localized protective response elicited by tissue damage caused by physical trauma, damaging chemical substances, or microbiological substances. Inflammation serves to destroy, reduce, or localize both damaging agents and tissues. Signs of inflammation are swelling/edema, redness, heat, pain, and changes in function [4]. Inflammation can be divided into acute and chronic inflammation. Acute inflammation lasts in short time and usually beneficial to the host. When inflammation persists for a long time, it can lead to various chronic diseases, such as arthritis, pancreatitis, metabolic diseases, and some types of cancer. Inflammation can exacerbate disease, which in turn exacerbates inflammation, creating a vicious cycle that poses challenges to treatment [5].

In general, anti-inflammatory treatment is carried out in three groups of drugs. The first line is non-steroidal anti-inflammatory drugs, the second line is steroid drugs and the third line is oral colchicine. The mechanism of action of non-steroidal anti-inflammatory drugs such as indomethacin and aspirin for the treatment is to block the formation of proinflammatory factors such as leukotrienes and prostaglandins [6].

1.3. Curcumin

Curcumin or diferuloylmethane is the main compound of yellow phytopolyphenol originating from the Zingirberaceae family, namely turmeric rhizome (Curcuma longa). The genus curcuma has 30 other species. The name curcuma comes from the Arabic word "turmeric" which means yellow. Turmeric contains three curcuminoid phytochemicals namely curcumin, bisdemethoxycurcumin and demethoxycurcumin, essential oils (natlantone, tumerone and zingiberone), protein, sugar, and resin. This component is also found in several other types of findings, such as temulawak. Curcuminoid is a potent antioxidant, beside that it also has other effect such as a hypocholesterolemic agent, cholagogue, choleretic, bacteriostatic, spasmolytic, anti-hepatotoxic, and anti-inflammatory. In Ayurvedic and Chinese medicine, turmeric rhizome is believed to be an anti-inflammatory drug, indigestion, liver disease and the treatment of skin diseases and can treat wounds [4].

Curcumin is a lipophilic polyphenol that almost insoluble in water, but quite stable in the pH of stomach. It is rapidly metabolized, conjugated in the liver, and excreted in the feces. Therefore, curcumin has limited systemic bioavailability. Phenolic compounds derived from herbs such as curcumin have shown anti-inflammatory activity in vitro and in vivo [7]. Based on the function above, this review will explain the mechanism of curcumin as an anti-inflammatory treatment in Covid-19 [6].

2. Methods

Article searches were conducted on three databases (PubMed, Sage Journals, and Nature Portfolio) with the keywords “Curcumin”, “Covid”, and “Inflammatory”, results in 97 articles were found with details: 45 articles from PubMed; 33 articles from Sage Journals; and the 19 articles from Nature Portfolio. Then the search results were filtered by title, abstract, year of publication, open access, and full text review. At the end of the screening, 5 relevant articles were obtained with the topic to be discussed. The articles obtained are then thoroughly reviewed.

3. Results and discussion

The focus of the discussion in this review is the anti-inflammatory effect of curcumin on Covid-19. We summarize the findings in table 1.

The coronavirus is the main source that causes SARS-CoV-2. It has a glycoprotein on the enveloped spike or protein S which will bind to the ACE2 receptor on the plasma membrane of human cells. After entering the cell, the virus will then release the RNA genome into the cytoplasm and the Golgi cells will then be translated into two lipoproteins and structural proteins to be able to replicate. When the virus enters the cell, the viral antigen will be presented to the

Antigen Presentation Cell (APC) which responds to the humoral and cellular immune system mediated by T cells and B cells. In patients infected by SARS-CoV-2, IgM will disappear on day-12 and IgG will last longer [3], [8].

Table 1 Findings

No	Authors	Article Title	Year	Type	Findings
1	Saeedi-Boroujeni A, Mahmoudian-Sani MR, Bahadoram M, Alghasi A.	COVID-19: A Case for Inhibiting NLRP3 Inflammasome, Suppression of Inflammation with Curcumin?	2021	Review Article	Curcumin can reduce the expression levels of NLRP3, IL-1β, IL-18 and caspase-1 and inhibit inflammation in inflamed organs (liver, lung, brain, and kidney), affects various pathways and molecules as it applies anti-inflammatory, antioxidant and anti-apoptotic properties without any particular side effects.
2	Peng Y, Ao M, Dong B, Jiang Y, Yu L, Chen Z, Hu C, Xu R.	Anti-Inflammatory Effects of Curcumin in the Inflammatory Diseases: Status, Limitations and Countermeasures	2021	Review Article	Curcumin has a good anti-inflammatory function by inhibiting the production of inflammatory mediators. Curcumin regulates NF-κB, MAPK, AP-1, JAK/STAT and other pathways. Curcumin supplements or adjuvant drugs have a significant therapeutic effect.
3	Kunnumakkara AB, Rana V, Parama D, Banik K, Girisa S, Henamayee S, Thakur KK, Dutta U, Garodia P, Gupta SC, Aggarwal BB.	COVID-19, cytokines, inflammation, and spices: How are they related?	2021	Review Article	Intervention with curcumin in infected models showed that it was successful in inhibiting inflammatory cells, MMPs, and cytokines. It is possible that the antiviral and immunomodulatory properties of curcumin may be beneficial for the treatment of diseases associated with SARS-CoV-2 and Covid-19.
4	Pawar KS, Mastud RN, Pawar SK, Pawar SS, Bhoite RR, Bhoite RR, Kulkarni MV, Deshpande AR.	Oral Curcumin With Piperine as Adjuvant Therapy for the Treatment of COVID-19: A Randomized Clinical Trial	2021	Clinical Trial	In a randomized clinical trial, it was found that the use of curcumin with piperine as an adjunct therapy in the treatment of COVID-19 can substantially reduce morbidity and mortality, reduce treatment costs, as well as the logistical burden of treating COVID-19 patients. The curcumin dose increase test was also found to be safe for use for 3 months. Curcumin can be a safe natural therapeutic option to prevent post-Covid thromboembolism.

5	Marín-Palma D, Tabares-Guevara JH, Zapata-Cardona MI, Flórez-Álvarez L, Yepes LM, Rugeles MT, Zapata-Builes W, Hernandez JC, Taborda NA.	Curcumin Inhibits In Vitro SARS-CoV-2 Infection In Vero E6 Cells through Multiple Antiviral Mechanisms	2021	In Vitro	In vitro studies found that curcumin affects the replication cycle of SARS-CoV-2 and exhibits a virucidal effect with independent antiviral effects on variants/strains and immune modulatory properties. Significant reductions in IL-1β, IL-6, IL-8, and MCP-1 were also found in PBMC (peripheral blood mononuclear cells) models pretreated with curcumin prior to infection of SARS-CoV-2, compared with infected cells only.

According to the CDC, Covid-19 patients in China consists of 81% with mild symptoms, 14% with severe symptoms and 5% in the critical level [5]. Patients with mild symptoms showed an immune response in the form of increase in CD-8 T cells, follicular T helper and Antibody Secreting Cells (ASCs) on day 7-9 until day 20. A progressive increase in IgM/IgG was also found. However, patients with mild symptoms did not find an increase in proinflammatory chemokines and cytokines. In patients with severe symptoms found a low lymphocyte count, as well as low monocytes, basophils, and eosinophils. There was an increase in pro-inflammatory mediators but decrease in T helper cells, T suppressor and T regulators [8].

Clinical evidence has revealed that patients infected with COVID-19 often exhibit elevated levels of cytokines referred to as “cytokine storm” or “cytokine release syndrome”. Abnormal levels of these cytokines are thought to correlate with severe deterioration of health conditions in infected patients. Therefore, suppressing the increased inflammatory response generated during COVID-19 has proven to be important in preventing disease severity as well as associated health complications [9].

The acute inflammatory response occurs to heal damaged tissue, when the body experiences injury, irritation, or infection. However, when that acute response is ineffective, the body resumes a chronic inflammatory response. Oxidative stress is a major contributor to the inflammatory response and physiological decline that characterizes aging and degenerative diseases. Immune cells use free radicals such as ROS (Reactive Oxygen Species) and RNS (Reactive Nitrogen Species) to eliminate viruses and bacterias that cause disease. Overproduction of free-radicals results in a state of oxidative stress, which damages polyunsaturated fats in lipoproteins and cell membranes and alters proteins such as DNA and RNA. This damage leads to impaired cellular function and inflammatory response that contributes to cellular damage, aging, and disease [7].

Inflammatory reactions that occur in the organs of COVID-19 patients can be caused by SARS-CoV-2 itself or the body's excessive immune reaction; In addition to inflammatory reactions in the lungs, inflammatory reactions also occur in the skin, blood vessels, nerves, heart, kidneys, hormone system, pancreas, eyes, immune system, and muscles and bones [10].

Inflammatory reactions that often occur in the skin are systemic vasculitis and erythema multiforme [11], [12]. Abnormalities that often occur in blood vessels due to inflammatory reactions due to infection with COVID-19 are Haemophagocytic Lympho-Histiocytosis (HLH) and Thrombotic Thrombocytopenic Purpura [10]. The neurological disorders caused by SARS-CoV-2 are very diverse and associated with nerve invasion or neurotrophic damage such as encephalopathy, encephalitis, and cerebrovascular disorders; in addition, brain damage due to inflammation such as Guillain-Barré Syndrome (GBS) or acute myelitis can also occur [13]. The lungs which are the main targets of SARS-CoV-2 often experience pneumonia and Acute Respiratory Distress Syndrome (ARDS) which is characterized by increased concentrations of cytokines. In some COVID-19 patients, increased troponin-I levels were found and there was myocardial interstitial infiltration by mononuclear cells and lymphocytes. Glomerulonephritis is a response that is often found in COVID-19 patients from an inflammatory reaction that occurs in the kidneys. The hormonal system can also be affected by inflammatory reaction that occurs due to SARS-CoV-2 infection, the reactions that often occur are hyperthyroidism and thyrotoxicosis which are characterized by low TSH and high T4 levels [10].

Acute pancreatitis also often happened in COVID-19 patients as an inflammatory reaction that occurs in the pancreas. In addition, eye complaints such as uveitis and conjunctivitis are often found in COVID-19 patients [14], [15], [16]. The problem with the greatest number related to inflammatory reactions in COVID-19 patients is the immune system, it is said that in pediatric patients, Multisystem Inflammatory Syndrome in Children (MIS-C) often occurs which resembles Kawasaki disease. Besides that, in female patients it is often found Systemic Lupus Erythematous (SLE), while other studies have also found many COVID-19 patients who have antiphospholipid syndrome [10], [17], [18]. The most common symptoms in COVID-19 patients is myalgia, which is an inflammatory reaction characterized by an increase in inflammatory markers and high levels of creatinine kinase [19], [20].

Cytokines have a role to coordinate anti-microbial effector cells and provide signals that regulate, enhance and terminate the immune response. Cytokines basically have a short half-life with the hope of not exerting excessive effects outside the lymphatic system and sites of inflammation. Abnormalities in the three cytokine functions in regulating the onset of inflammation, increasing the response according to the severity of the infection and stopping the inflammatory process, cause cytokines to not work as they should. Regulatory cells and anti-inflammatory cytokines, such as IL-1RA and IL-10, also have an important role in the occurrence of cytokine storms. Cytokines that play a role in the inflammatory process are; IL-1, IL-2, IL-6, IL-9, IL-10, IL-12, IL-17, IL-18, IL-33, IFN-γ, TNF, GM-CSF and VEGF [21].

Excessive circulating cytokines can cause cell death and tissue damage while activated macrophages can cause erythro-phagocytosis and anemia. The effects of anemia, altered vascular hemostasis and cytokine-induced damage can cause multiple organs damage. Signs that arise in complications of cytokine storm are characterized by the development of Disseminated Intravascular Coagulations (DIC), capillary leak syndrome and decreased blood pressure due to epithelial damage and changes in vascular hemostasis [22].

Curcumin exerts an anti-inflammatory effect by regulating inflammatory signaling pathways and inhibiting the production of inflammatory mediators. Curcumin binds to Toll-like receptors (TLRs) and regulates nuclear factor kappa-B (NF-κB), Mitogen-activated protein kinases (MAPK), Activator Protein 1 (AP-1) and other signaling pathways. Curcumin can also control inflammation through the Janus kinase/Signal transducer and activator of transcription (JAK/STAT) pathway [23]. Inhibition of these pathways will ultimately suppress gene expression for inflammatory cytokines such as IL-1, IL-6, IL-8, and TNF- α [24].

One of the inflammatory cells that plays a role in many inflammatory diseases is NOD-like receptor pyrin domain-containing 3 (NLRP3). Curcumin is able to directly limit NLRP3 assembly or through inhibition of NLRP3 activation by inhibiting K(+) efflux, intracellular ROS production and cathepsin B release, which are all required to activate the NLRP3 inflammasome [23], [25].

Several investigators have proposed that TGF-ß could be a good therapeutic target for COVID-19[26], [27]. Coronavirus when enters cells, it damages the function of TGF-ß expression to be excessive, thus impairing cell cycle arrest. Curcumin can inhibit TGF- ß1 and reduce the production of proinflammatory cytokines such as TNF-α and MPC-1.

Based on Pawar et al (2021), a randomized clinical trial was conducted with the administration of curcumin and piperine orally as adjuvant therapy alongside other conventional Covid-19 therapies. Administration of curcumin in combination with piperine aims to increase the bioavailability of curcumin which is low because it is metabolized rapidly [28], [29]. From this study, it was found that in the intervention group earlier in symptom recovery (fever, cough, sore throat, shortness of breath), reduced the need for medical interventions such as oxygen administration and ventilator installation, substantially reduced the duration of hospitalization in patients with moderate and severe symptoms, also found a lower mortality rate [30].

In addition to having an anti-inflammatory effect, a potential antiviral effect was also found in the administration of curcumin therapy. In an in vitro experiment using Vero E6 cells, pre- and post-infection therapy for SARS-CoV-2 using curcumin showed an antiviral effect of up to 99% in the D614G strain and 99.8% in the Delta variant. Curcumin can also inhibit the replication of the D614G strain by pre-infection and post-infection treatment. In addition, curcumin showed a virucidal effect against the D614G strain and the Delta variant [31]. This finding needs to be tested further using an in vivo model to be developed further.

The known pathophysiology of COVID-19 primarily involves life-threatening inflammatory reactions, cytokine storms, and coagulopathy. Inflammation is the first symptom observed in this disease. Viral infection and inflammation-induced hemoconcentration and difficulty in oxygen and carbon dioxide exchange (apparently mimicking polycythemia vera) might be the major causes of hypoxia. Curcumin has anti-inflammatory activity and exerts an antithrombotic effect

through inhibition of thrombin and FXa [32]. This can reduce the viscosity of the blood and thus the risk of developing blood clots and related complications. Therefore, curcumin has great potential as an anti-inflammatory drug in the treatment of COVID-19. Curcumin showed good efficacy when combined with other antivirals and anticoagulants. Like oral aspirin and clopidogrel, which are used as adjunctive therapy with thrombolytic agents for the treatment of myocardial infarction, oral curcumin is likely to help relieve COVID coagulopathy when given with or without heparin. In addition, the antibacterial and antifungal effects of curcumin may play a role in preventing secondary infection and thereby promoting early recovery [30].

4. Conclusion

This review indicates that curcumin has a great potential anti-inflammatory effects to treat COVID-19 cases. Previous studies on other inflammatory diseases have shown an anti-inflammatory effect on curcumin, the same results were also found in in vitro, in vivo, and clinical trials on Covid-19 patients. The findings of other effects such as antibacterial and antifungal on curcumin are also useful for preventing secondary infections. The use of curcumin as an adjunct drug in the treatment of Covid-19 also has other potential benefits such as reducing treatment costs, and speeding up recovery, and preventing post-covid thromboembolism.

Compliance with ethical standards

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Disclosure of conflict of interest

I and my co-authors have no conflict of interest associated with this publication. The manuscript has also been read and approved for submission by all of my co-authors.

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