

Nanoencapsulation of Curcumin compounds from Curcuma plants (*Curcuma xanthorrhiza*) as an anticoagulant therapy in Covid-19 patients

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ABSTRACT

Introduction: The COVID-19 is brought about by the SARS-CoV-2 virus (Severe Acute Respiratory Syndrome Coronavirus-2). This pandemic has become a problem in various parts of the world due to the increasing number of positive COVID-19 cases. Severe COVID-19 patients often experience coagulopathy such as thrombosis and venous thromboembolism, which are associated with increased mortality. COVID-19 patients who have coagulopathy have increased D-dimer concentrations, prolonged prothrombin time (PT) or activated partial thromboplastin time (aPTT), increased fibrinogen, and thrombocytopenia. The objective of this study is to find an alternative solution for COVID-19 patients who have coagulopathy using the literature review method by searching the data from in vitro, in vivo, and clinical reports by analyzing the potential of the curcumin compound from ginger as an anticoagulant therapy in Covid-19 patients through its thrombosis, platelet, and anti-inflammatory mechanisms.

Main Text. The nanoencapsulation of curcumin from Curcuma plants (*Curcuma xanthorrhiza*) can be an alternative prophylactic anticoagulant for COVID-19 patients. This research uses a qualitative method of conceptual analysis, where the focus of the research is based on pre-existing concepts, which are then understood and developed so that they can be described clearly and can be implemented in the field. The result is curcumin can inhibit the pathways of blood coagulation, so it could be the key to reducing mortality.

Conclusion: Nanoencapsulation has proven to be suitable for alternative application in COVID-19 patients considering bioavailability, effectiveness, and minimum side effects.

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INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic has become a problem in various parts of the world due to the increasing number of positive COVID-19 cases reaching 190,779,472 cases and claiming 173,852,764 lives based on the latest data on July 18, 2021 (Worldometer, 2021). This COVID-19 is brought about by the SARS-CoV-2 virus (Severe Acute Respiratory Syndrome Coronavirus-2), which first appeared in Wuhan in December 2019 (Peretto et al., 2020). The infection of the SARS-CoV-2 virus can cause various symptoms, ranging from mild, moderate, severe, and even asymptomatic. Some of the common symptoms of COVID-19 are fever, cough, shortness of breath, headache, sore throat, rhinorrhea, and others (Gennaro et al., 2020). Other than that, several studies have shown that severe COVID-19 patients often experience

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coagulopathy such as thrombosis and venous thromboembolism, which are associated with increased mortality (N. Chen et al., 2020; Huang et al., 2020; Tang et al., 2020a).

Based on the study of Cui et.al, the incidence of venous thromboembolism in severe COVID-19 patients about 25% (20 of 81 patients) are treated in the intensive care unit. (Cui et al., 2020) Coagulopathy in COVID-19 patients is related to the presence of the angiotensin-converting enzyme 2 (ACE2) receptor, which serves as the primary receptor for SARS-CoV-2. This receptor is widely expressed in alveolar epithelial cells of the lungs, heart, vascular endothelium, kidney, and gastrointestinal tract (Zaim et al., 2020). Coagulation in severe COVID-19 patients occurs when the ACE2 receptor links to the S protein of the SARS-CoV-2 virus (Nilea et al., 2020).

The aggregation of SARS-CoV in the lungs disrupts alveolar epithelial and endothelial cells. In addition, this aggregation also causes infiltration of inflammatory cells, resulting in pro-inflammatory cytokines such as IL1, IL-6, and TNF α , and others. This causes an exaggerated immune response resulting in a systemic cytokine storm that causes the systemic inflammatory response syndrome (SIRS). This response results in systemic endothelial injury and a hypercoagulable state resulting in an increased risk of systemic macrothrombosis and microthrombosis. (Joly et al., 2020) COVID-19 patients who have coagulopathy have increased D-dimer concentrations, prolonged prothrombin time (PT) or activated partial thromboplastin time (aPTT), increased fibrinogen, and thrombocytopenia (Terpos et al., 2020).

To treat coagulopathy, current guidelines recommend prophylactic anticoagulation such as heparin in all hospitalized COVID-19 patients except contraindicated and outpatients (Barnes et al., 2020; Godino et al., 2021). However, the use of heparin as a prophylactic anticoagulant has side effects, such as bleeding and allergies (Sakti et al., 2018a). To overcome this problem, researchers are looking for alternative anticoagulants derived from the Curcuma plant (*Curcuma xanthorrhiza*). *Curcuma xanthorrhiza* contains xanthorrhizol, curcumin, and several volatile substances (Cheah et al., 2009; Jantan et al., 2012; Mahmud, 2012). Based on the research of Kim DC et.al, curcumin can act as an anticoagulant because it can inhibit thrombin and factor Xa activation without the help of thrombin III in human blood plasma. In addition, curcumin and its derivatives can prolong Prothrombin Time (PT) and activate partial Thromboplastin Time (aPTT) (Sakti, Roslaeni and Harihardjaja, 2018). The use of curcumin is very safe for humans even if taken in high doses (12 g/day). Then, to increase the clinical potential of curcumin, formulation strategies can be carried out, such as nanoparticles to increase the solubility, stability, and proper and selective transport of curcumin to the target site to improve pharmacokinetics (Akolade et al., 2018; Oliveira et al., 2018).

This research is a literature review of journals that are relevant to the topic raised. Authors used literature search engines from indexed journal databases, nationally and globally, including Portal Garuda, Google Scholar, and Pubmed. The inclusion criteria of articles used were in English, original research or meta-analysis, from indexed journal publication, and related to the topic. The exclusion criteria from data collection are those that do not match the inclusion criteria.

MAIN TEXT

Blood Clotting Problems as a Complication in Covid-19 Patients

COVID-19 sufferers display thrombotic complications in addition to pneumonia, respiratory failure, sepsis, or more severe conditions (Cui et al., 2020; Katsoularis et al., 2022a). An inherent trait of COVID-19 illness is the connected coagulopathy linked with heightened levels of

circulating D-dimer concentrations. D-dimer is the product of fibrin breakdown found within the bloodstream after blood clot dissolution (Asakura & Ogawa, 2021; Di Tano et al., 2022). The International Society of Thrombosis and Hemostasis has outlined a protocol for evaluating D-dimer, prothrombin time, platelet count, and fibrinogen in all COVID-19 patients (Karsy et al., 2020). Notably elevated D-dimers, extended prothrombin time, increased platelet count, and elevated fibrinogen serve as guiding indicators for the care of individuals with COVID-19. Two theories elucidate the hypercoagulable state and secondary hyperfibrinolysis in COVID-19-associated coagulopathy (Pavoni et al., 2020).

One posits heightened levels of pro-inflammatory cytokines (IL-6, IL-1, and TNF α) contributing to microvascular lung impairment and endothelial dysfunction, consequently leading to hemostatic irregularities and pulmonary thrombosis (Katsoularis et al., 2022b). An alternative hypothesis suggests that the virus directly or indirectly affects the coagulation pathway, resulting in systemic thrombosis. The compromised endothelial function triggers clot-related complications such as heart attacks, strokes, and thromboembolism (Paliogiannis et al., 2020a; Zhou et al., 2020a).

During COVID-19 infection, the coronavirus infiltrates the systemic circulation and attaches to endothelial cells that line blood vessels and express ACE2 receptors. This attachment expedites the uptake of the virus, initiating infection and harm to the vessel lining. Impairment of blood vessels prompts constriction, exacerbating the decrease in blood flow to the injury location (Biswas et al., 2021).

Vasoconstriction and ACE2 expression share an inverse relationship. During systemic infection, ACE2-expressing endothelial cells within blood vessels can attach to the viral spike protein, resulting in ACE2 becoming inaccessible. The renin-angiotensin-aldosterone system (RAAS) can instigate the progression of COVID-19 by prompting the expression of tissue factor (TF) and plasminogen activator inhibitor-1 (PAI-1) through angiotensin II (Ag II) stimulation in cells. This, in turn, leads to the formation of microthrombi within the endothelium of COVID-19 patients. Angiotensin II (Ag II) influences the central nervous system (CNS) to increase vasopressin production, culminating in blood vessel constriction. The depletion of ACE2 due to SARS-CoV-2, imbalances in PAI-1/tPA, and heightened coagulation tendencies collectively contribute to tissue damage and the occurrence of strokes (Hess et al., 2020).

The emergence of thrombotic issues in microvasculature suggests a strong interaction between SARS-CoV-2 and the coagulation system. Instances of platelet-fibrin clots have been documented in over 80% of lung autopsies, particularly within minor pulmonary vessels. The existence of antiphospholipid antibodies represents a significant complication, notably triggering thrombotic strokes, particularly in the case of younger adolescents (Y. Zhang et al., 2020).

Al-Samkari et al indicated that increased D-dimer levels upon admission were indicative of the likelihood of severe illness and mortality, alongside bleeding and thrombotic issues. Indicators of inflammation such as CRP and ESR were similarly linked to thrombosis, and notable elevations in various coagulation and inflammation markers were tied to heightened chances of severe illness and death. However, the model predicting mortality displayed notable uncertainty, depicted by broad confidence intervals. Moreover, a substantial correlation was observed between D-dimer levels and each of the assessed inflammatory markers (Al-Samkari et al., 2020).

Anticoagulant Effect of Curcumin Compounds from Curcuma in Covid-19

For centuries, the extract derived from the rhizomes of the Curcuma plant has been extensively utilized worldwide as a culinary addition. The usage of Curcuma plant extract or Curcuma plant butter as a spice and home remedy has long been acknowledged as safe. Human clinical trials have substantiated the safety and tolerance of the Curcuma plant (Keihanian et al., 2018; Omidian et al., 2023; Rajkumari & Sanatombi, 2018). Across numerous prior investigations, Curcuma plant extract has been employed as an anti-inflammatory agent to address issues like flatulence, colic, toothache, chest pain, menstrual difficulties, and gastrointestinal and hepatic disorders. The key polyphenolic compound is curcumin. In terms of its mechanism of action, curcumin displays a range of metabolic, cellular, and molecular functions, encompassing its anticoagulant attributes. The researchers delved into the antithrombotic capabilities of curcumin, as well as its potential to mitigate thrombosis by modulating platelet count, D-dimer levels, and plasminogen activator inhibitor-1 in mice (L. Zhang et al., 2020a).

Human plasma was employed to assess the anticoagulant attributes of curcumin through aPTT and PT measurements, revealing that curcumin substantially extended both aPTT and PT. To validate these findings obtained in a laboratory setting, the duration of bleeding from the tail was gauged in live subjects. (Ambreen et al., 2021) Furthermore, curcumin notably prolonged the bleeding duration from the tail. Before this study, curcumin had demonstrated efficacy as an anticoagulant by inhibiting thrombin or FXa. Curcumin's ability to impede FXa production and subsequent thrombin generation lends support to its anticoagulant effects. As commonly understood, FXa does not influence platelet activation. However, once it assembles into the prothrombinase complex, it initiates a substantial thrombin production (Grobler et al., 2020a; Iba et al., 2020a).

Based on the results that curcumin can inhibit the production of FXa and thrombin, its anticoagulant effectiveness commences by inhibiting these factors. It is established that TNF- α can trigger activation of JNK, NF- κ B, and ERK within human endothelial cells. The outcomes demonstrated that the inhibitory effects of ERK and curcumin on TNF- α -induced PAI-1 secretion were cumulative (Kim et al., 2012). These outcomes imply the involvement of the NF- κ B and JNK pathways in curcumin-mediated suppression of TNF- α -induced PAI-1 expression in HUVEC. Consequently, these findings suggest that curcumin diminishes PAI-1 levels by curtailing the NF- κ B and JNK pathways (Rattis et al., 2021). Additionally, curcumin operates as an antioxidant in a secondary mode of action. The hydrogen bond interaction between the phenolic OH and o-methoxy group in curcumin compounds substantially influences the OH bond energy and the removal of H atoms by radicals, endowing it with enhanced free radical scavenging abilities.

Furthermore, curcumin demonstrates heightened efficacy as an inhibitor of NF- κ B activation, a pivotal aspect of its anticoagulant attributes, and warrants further assessment (H. W. Chen et al., 2007). The anti-inflammatory effects of curcumin result from the activation of peroxisome proliferator-activated receptor- γ (PPAR- γ) (Singgih Wahono et al., 2017). The results from Rusdiana et al also indicate that administration of turmeric increases the steady-state concentration of warfarin in rats. Theri study demonstrates that coadministration of turmeric extract to rats can alter the pharmacokinetics of warfarin enantiomers, particularly at high doses (Rusdiana et al., 2021).

In a recent study, it was stated that the death rate due to COVID-19 was caused by hemostasis problems, especially blood hypercoagulation. Elevated D-dimer concentrations are anticipated to serve as a prominent indicator of predisposition to thrombosis and an unfavorable

prognostic factor (Paliogiannis et al., 2020b). Augmented platelet activation and identifiable viral RNA in the bloodstream are linked to escalated platelet hyperactivity, culminating in atypical blood coagulation. These factors are interconnected with thromboembolic consequences observed in individuals afflicted by COVID-19 (L. Zhang et al., 2020b; Zhou et al., 2020b). The following signs of hypercoagulability were observed in these patients: prolongation of prothrombin time (PT), activated partial thromboplastin time (APTT), and elevated levels of D-dimer and other fibrin degradation products (FDP) (Tang et al., 2020b).

Endothelial cells exhibit receptors essential for the binding and invasion of cells by SARS-CoV-2, leading to cellular harm and programmed cell death. Impairment of the vascular endothelium unveils procoagulant elements like collagen and von Willebrand factor (vWF), initiating the secretion of tissue factor (TF) (Grobler et al., 2020b; Iba et al., 2020b). Platelets feature distinct receptors for these substances, comprising glycoprotein VI (GPVI) attached to subendothelial collagen, and glycoprotein (GP) Ib-IX-V connected to von Willebrand factor (vWF) (Grobler et al., 2020a).

Offering additional substantiation of curcumin's advantages, a 10 mg curcumin injection administered over 15 days effectively diminished fibrin deposition within kidney glomeruli. Instances of coagulation activation and thrombosis are prevalent among individuals grappling with COVID-19, potentially leading to severe harm. In a clinical study, reducing these fibrin deposits was achieved by administering a 10 mg curcumin injection (H. W. Chen et al., 2007; Rattis et al., 2021).

Natural compounds Curcumin and ibuprofen work well for many people. This makes them promising research about the COVID-19 disorder hemostatic. Both are associated with cell death and neutrophil activation. This leads to increased inflammation as well as cell death via NETosis (Schönrich & Raftery, 2016), impairments in the breakdown of neutrophil extracellular traps (NETs) resulted in the blockage of lung blood vessels. This culminates in organ injury and the creation of blood clots and thrombi. Both platelet-dependent and independent pathways contribute to NET formation via the formation of platelet-derived structures called thrombi (Gómez-Moreno et al., 2018; Jiménez-Alcázar et al., 2017).

At autopsy, examinations of lung tissue specimens obtained from patients with acute respiratory distress syndrome and sepsis unveiled constituents of neutrophil extracellular traps (NETs) within the evident clots. These observations underscore the potential for NETs to generate intravascular clots within the human system (Jiménez-Alcázar et al., 2017). The products released by NETs can also be cytotoxic to endothelial cells. This can cause endothelial cells to die off, which subsequently supports the formation of more NETs and a thrombo-inflammatory response (McFadyen et al., 2020a).

Antiplatelet Effect of Curcumin Compounds from Curcuma in Covid-19

Curcumin is critical to the antiplatelet effect of the active ingredient in the drug. It reduces the expression of P-selectin and GPVI, which are critical for platelets to adhere to the vascular endothelium and sub-endothelium (Grobler et al., 2020a). This prevents platelets from attaching to the vascular wall and leads to a decrease in their function and neutrophil migration into the body. In test tubes and animal models, curcumin has demonstrated significant effects on neutrophilic infiltration (McFadyen et al., 2020b).

Additionally, curcumin treatment has been proven to inhibit NETs, which are crucial for neutrophilic infiltration in LPS-induced mouse models of air pouch inflammation (Antoine et al.,

2013). Curcumin administration in an in vivo model of disseminated intravascular coagulation (DIC), led to a decrease in circulating levels of TNF- α . This led to lower numbers of neutrophils being activated, which decreased the occurrence of NETS.(H. W. Chen et al., 2007) Curcumin's effect on P-selectin expression may be one of the key mechanisms behind this decrease. Platelets use P-selectin to attach to neutrophils, increasing their chances of being activated (McFadyen et al., 2020a).

Nanoencapsulation of Curcumin Compounds from *Curcuma xanthorrhiza*

The nanotechnology application is carried out to increase solubility, stabilize thermal conditions, and facilitate the digestibility of compounds contained in the encapsulated material. The nanoencapsulation process is expected to protect sensitive or unstable core materials from environmental influences before use, increase shelf life by preventing degradation reactions (oxidation, dehydration), and reduce the irritating properties of core materials to the stomach and digestive tract (H. W. Chen et al., 2007; Schönrich & Raftery, 2016).

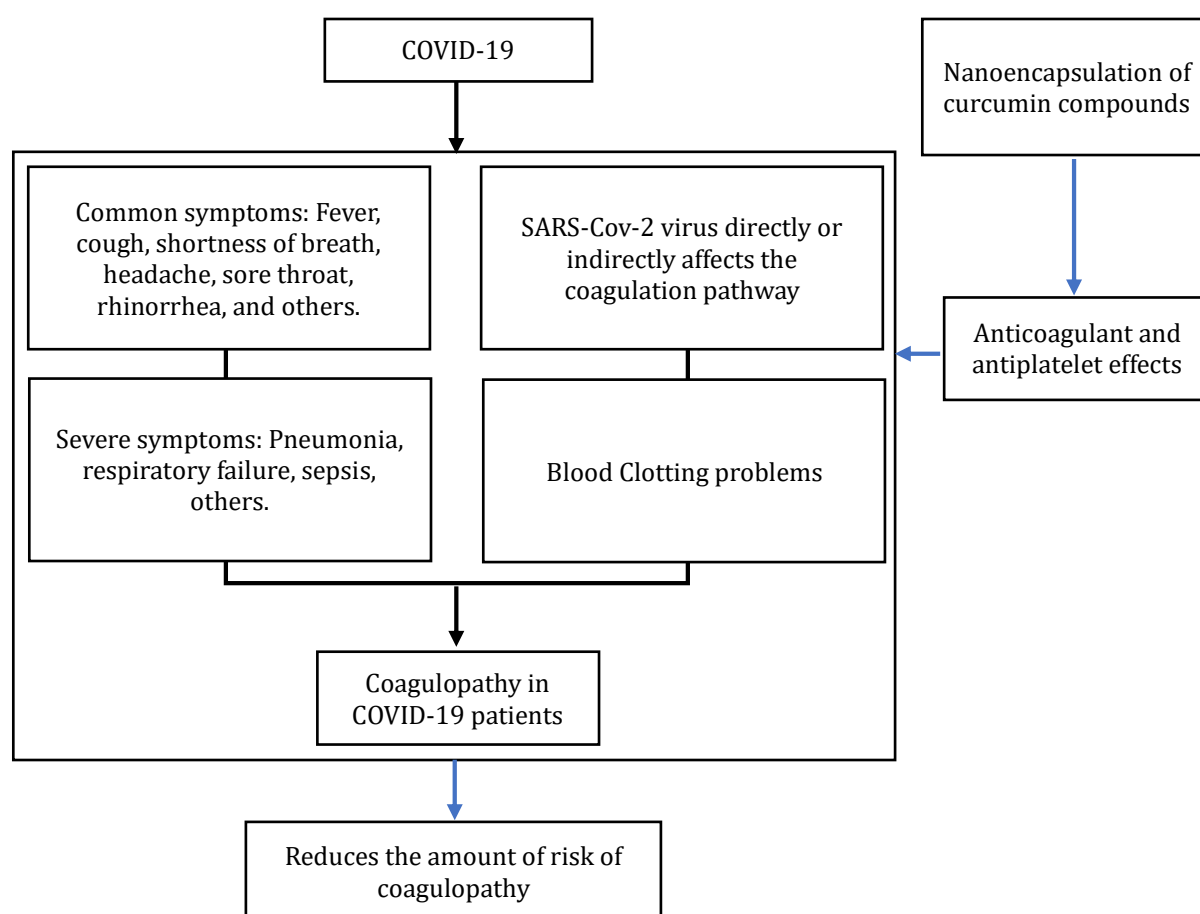


Figure 1. Effect of Nanoencapsulated Curcumin Compounds to Coagulopathy Complication In COVID-19 Patients

The nanoencapsulation method can improve the solubility, dispersion ability, and flow properties of the core ingredients to prevent incompatibility between the compositions in the preparation and of course, cover unpleasant odors and tastes to increase the effectiveness and interest of patients to consume them (Jiménez-Alcázar et al., 2017). Santos et al. have reported that encapsulated curcumin exhibits biological activity in aqueous media (without the addition of hydrophobic solvents), exerts antioxidant and cytotoxic effects, and acts on cholinergic and endogenous antioxidant systems (Dos Santos et al., 2019).

On the other hand, oral curcumin has low bioavailability and is rapidly metabolized and excreted. Peng et al. found that curcumin nanoparticles have a high surface area to volume ratio, which is achieved by nanocarriers, and can increase the solubility and dissolution rate of the drug (Peng et al., 2018). In addition, small particle size can prolong the residence time of drugs in the systemic circulation, change drug distribution, and enable targeted delivery and transport of drugs across barriers. For the above reasons, encapsulating curcumin in nano formulations can effectively improve its solubility and bioavailability (Y. Chen et al., 2020; Mohanty & Sahoo, 2010).

Nano-encapsulated curcumin has proven to be suitable for alternative applications in COVID-19 patients considering its bioavailability, effectiveness, and minimum side effects. Materials can be presented in various forms and appearances according to therapeutic goals, targets, and consumer interests.

CONCLUSION

To summarize, this review of existing literature demonstrated that curcumin effectively hindered both the extrinsic and intrinsic pathways of blood clotting by suppressing the production of FXa and thrombin, as confirmed through in vitro and in vivo investigations. These findings build upon prior research and offer insights that could be valuable in developing well-considered pharmacological approaches to manage or preempt vascular disorders by modulating thrombin production. Consequently, the latent efficacy of curcumin as an antithrombotic agent for addressing coagulopathies linked to COVID-19 holds promise and warrants further exploration. Nano-encapsulated curcumin improves the solubility, dispersion ability, and flow properties of the core ingredients. It has proven to be suitable for alternative application in COVID-19 patients considering bioavailability, effectiveness, and minimum side effects.

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