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Curcumin: A Review on its Potential Benefits on COVID-19 Clinical Manifestations

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A B S T R A C T

Coronavirus disease, abbreviated as COVID-19, is a novel infectious disease caused by the SARS-CoV-2 virus and is characterized by lymphopenia, pneumonia, a cytokine storm (CS), and lymphocytes that are functionally exhausted. Although the virus primarily manifests itself as a respiratory illness, it also affects other major organs of the body due to its ability to bind to angiotensin-converting enzyme 2 (ACE2) receptors, which are spread all throughout the tissues of the body. Currently, no specific antiviral treatment has been identified, but clinicians are exploring herbal constituents as an approach. In treating COVID-19 symptoms, a promising candidate for studies is curcumin, whose anti-inflammatory tumor-suppressing efficacy and anti-oxidative properties have been examined previously. As a result, it could be used as a viable therapeutic method for lung injury and other respiratory illnesses. Moreover, it has been recommended as a treatment for liver and other digestive problems as it aids in decreasing the progression of gastrointestinal malignancies. The potential of curcumin in alleviating symptoms associated with COVID-19 can give new hope for prevention and treatment, which the world has longed for. Collectively, this paper seeks to dissect the pathologic effects of COVID-19 in the body, specifically in the lungs, gastrointestinal tract, and blood, which may be mitigated with the use of curcumin

Keywords:COVID-19, turmeric, curcumin, lungs, gastrointestinal tract, blood coagulation

1. Introduction

A series of acute respiratory illnesses rapidly spread from Hubei Province, China, to other nearby areas in December 2019. It was later uncovered that a novel coronavirus caused the reported symptoms. By January 2020, the World Health Organization (WHO) classified the outbreak as a public health emergency as the virus rapidly spread to other countries, causing an expeditious growth in the number of infections. Come February 2020, the virus, now officially named the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) by the International Committee on Taxonomy of Viruses, has infected almost 50,000 people worldwide [1][2]. As of today, there have been almost 281 million confirmed cases of COVID-19, with a total of 5.4 million deaths worldwide [3].

Respiratory symptoms predominantly characterize COVID-19 symptoms. Such symptoms consist of cough, dyspnea, and a runny nose. However, recent cases also describe gastrointestinal symptoms. In some cases, digestive manifestations like nausea, vomiting, and decreased appetite are noted as early COVID-19 symptoms. In severe cases, the virus affects multiple organs, such as the brain, heart, kidneys, and liver [4]. This shows that apart from the respiratory system, other organs may be affected by COVID-19.

Until now, no definite antiviral therapy is available to treat COVID-19. Hence, the predominant treatment approach to the virus is focused on symptom management [5]. In preventive and supportive approaches, various polyphenolic compounds extracted from natural sources were detected, and one of the natural compounds being investigated is curcumin, the main constituent of turmeric [6].

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The growing evidence of curcumin's therapeutic properties suggests that curcumin is a potential supportive and preventive treatment option for COVID-19. More than 300 clinical trials have demonstrated the protective effects of curcumin against different conditions, including cardiovascular, pulmonary, inflammatory, liver, and neurological disease [7]. Moreover, curcumin has already been approved by the United States Food and Drug Administration (FDA) as "Generally Recognized as Safe" [8]. Although the potential role of curcumin has been demonstrated by numerous studies, the main objective of this review is to elucidate the pathologic conditions in the lungs, gastrointestinal tract, and blood coagulation of COVID-19 patients which may be alleviated with curcumin.

2. Methods

This article review utilizes recovered studies and peer-reviewed articles from the different journals in WebMD, NHLBI, MedRxiv, The Lancet, CDC, DOI, LPI, and WHO. The American Journal of Gastroenterology, American Journal of Respiratory Cell and Molecular Biology, Journal of Ethnopharmacology, New England Journal of Medicine, The Journal of Pathology, Journal of Virology, Journal of Thrombosis and Haemostasis, and DrugBank were also selected for the search of the articles. The search for studies started from November to December 2021. The explored topics mainly focused on how the virus affects the lungs, gastrointestinal tract, and blood coagulation, as well as the health-related benefits of curcumin to COVID-19 symptoms. All the articles were carefully reviewed and analyzed.

2.1. The Effect of COVID-19 on the Major Organs of the Body

COVID-19 often presents itself as a flu-like illness in patients developing symptoms in response to the virus [9]. Although the virus mainly affects the respiratory system, it affects any other organ due to its primary mechanism of binding to angiotensin-converting enzyme 2 (ACE2) receptors found in the heart, blood vessels, liver, kidneys, and other tissues. Because of this, patients with COVID-19 can die due to single or multiple organ failure [4][9]. Aside from binding to the ACE2 receptors, coronaviruses such as the COVID-19 reduce the expression of ACE2 receptors in these organs, which consequently contributes to organ failure [10].

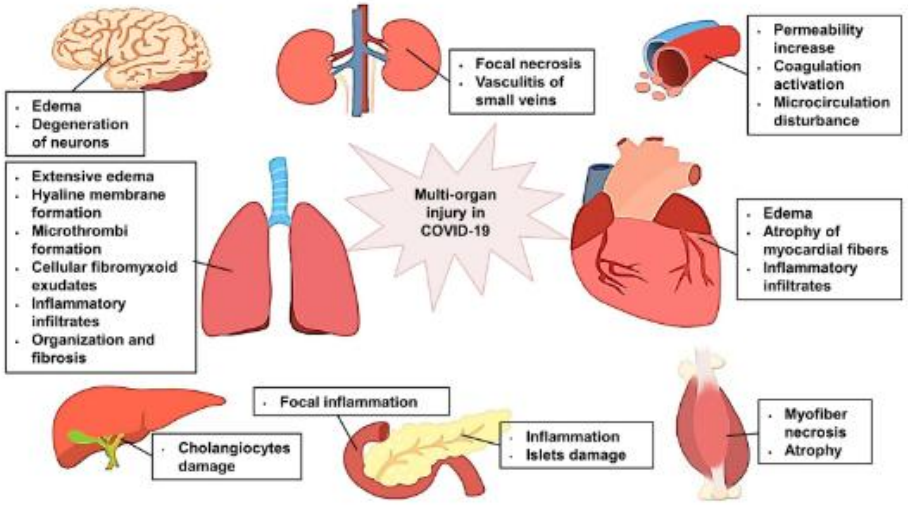

Fig. 1: The main organs affected by COVID-19 [11]

For this paper, the effects of the virus in the lungs, gastrointestinal tract, and blood shall be further examined.

2.1.1Respiratory manifestations in COVID-19 patients

Most symptomatic patients present with respiratory manifestations such as dry cough and shortness of breath, which are presently used to select candidates for viral testing [12]. Studies show that about 80 percent of patients experience upper respiratory diseases and may be treated with conservative symptomatic therapy at home. On the other hand, the lower respiratory tract of some may also be involved [9][13]. Other respiratory symptoms include loss of smell, difficulty breathing, chest pains, and a congested or runny nose [14].

Apart from causing conspicuous respiratory symptoms, the virus also manifests in other ways. A German study involving young to middle-aged adults showed that pharyngeal virus shedding was present during the first week of symptom onset, while sputum viral shedding continued even after the symptoms had subsided [9]. In autopsy studies, infected people show classic diffuse alveolar damage, pulmonary edema, arteriolar thrombi, acute fibrinous and organizing pneumonia, airway inflammation, and vascular angiogenesis [15][16][17][18][19].

The receptors involved explain the mechanism of the virus' proliferation in the lungs. First, the virus enters the respiratory tract via inhalation. The inhaled virus then replicates in the nasal cavity [20]. Thereafter, the virus enters the lungs via the ACE2 receptors, the specific receptor for the virus. These receptors are mainly found on type II alveolar epithelial cells found in the lungs, which explains why the lungs are the virus' main target [21]. Although some cells express other coronavirus receptors such as aminopeptidase N and dipeptidyl peptidase 4 (DPP4), they are impermeable to the virus [22][23].

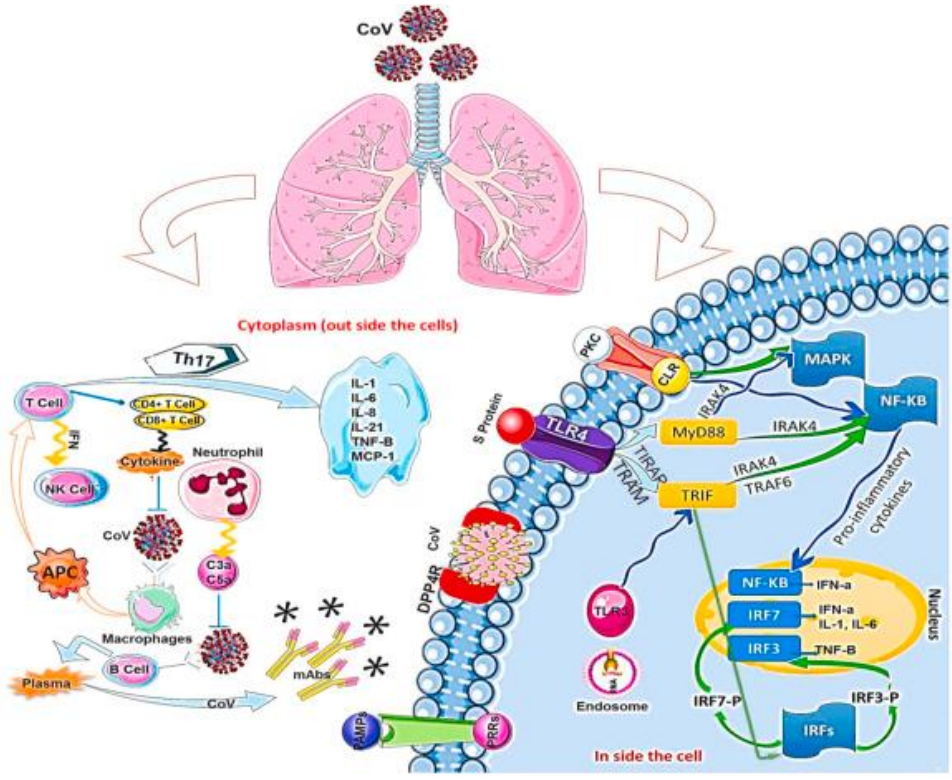

Fig. 2: COVID-19 mechanism of action in the lungs [24]

As the virus enters pulmonary cells, it rapidly replicates itself, resulting in an immune complex-induced inflammation. Normally, ACE2 receptors aid in reducing inflammation, but because the virus binds to such receptors, the inflammatory response is not inhibited. This continued inflammation leads to fluid build-up, lung tissue scarring, and eventually lung damage [25]. The virus in alveolar cells may cause apoptosis, which subsequently causes the release of pulmonary toxins affecting the adjacent cells. This leads to the disease's progression to acute respiratory distress syndrome or ARDS [26].

COVID-19 is highly transmissible via the respiratory route, and the virus predominantly manifests as respiratory disorders and complications. Thus, the appropriate symptomatic management of the disease is imperative not only to curb viral transmission but also to effectively improve outcomes in COVID-19 patients.

2.1.2 Gastrointestinal manifestations in COVID-19 patients

Although the indisputable presentation of the COVID-19 are flu-like symptoms like fever, dry cough, sore throat, runny nose, and dyspnea, COVID-infected patients may also present with appetite loss, the most common digestive disturbance, and other digestive symptoms like diarrhea, nausea, vomiting, acid reflux, and abdominal pain [27]. The American Journal of Gastroenterology reports that out of the 206 examined patients, a total of 117 patients experienced gastrointestinal disturbances. Forty-eight patients experienced digestive disturbances alone, while 69 patients had them alongside respiratory manifestations [28]. Another study reported that more than 61 percent of COVID-19 patients had gastrointestinal symptoms [29].

Studies indicate that the link between COVID-19 and gastrointestinal symptoms is mainly due to the mechanism of the virus' propagation in the body. To reiterate, the virus crosses cells by binding to ACE2 receptors, which are abundant in the gastrointestinal tract and are important for the regulation of intestinal inflammation [28][30]. Aside from ACE2 receptors, the virus also depends on transmembrane protease serine 2 (TMPRSS2), which is crucial for the fusion of viral cells with cellular membranes. TMPRSS2 proteins are found in the ileum and the colon, which means that COVID-19 can attack enterocytes or intestinal absorptive cells of the gastrointestinal tract [31][32].

Selecting candidates for COVID-19 testing is chiefly based on the presence of respiratory manifestations. With this, there is a possibility that a portion of COVID-19 patients remain undiagnosed and may not get the treatment needed. Several studies also indicate that some patients present with only digestive disturbances [28][33]. Hence, digestive disturbances as atypical COVID-19 manifestations must be promulgated not only to prevent unconscious transmission of the virus but also to deliver the appropriate symptomatic treatments and management in patients experiencing gastrointestinal symptoms.

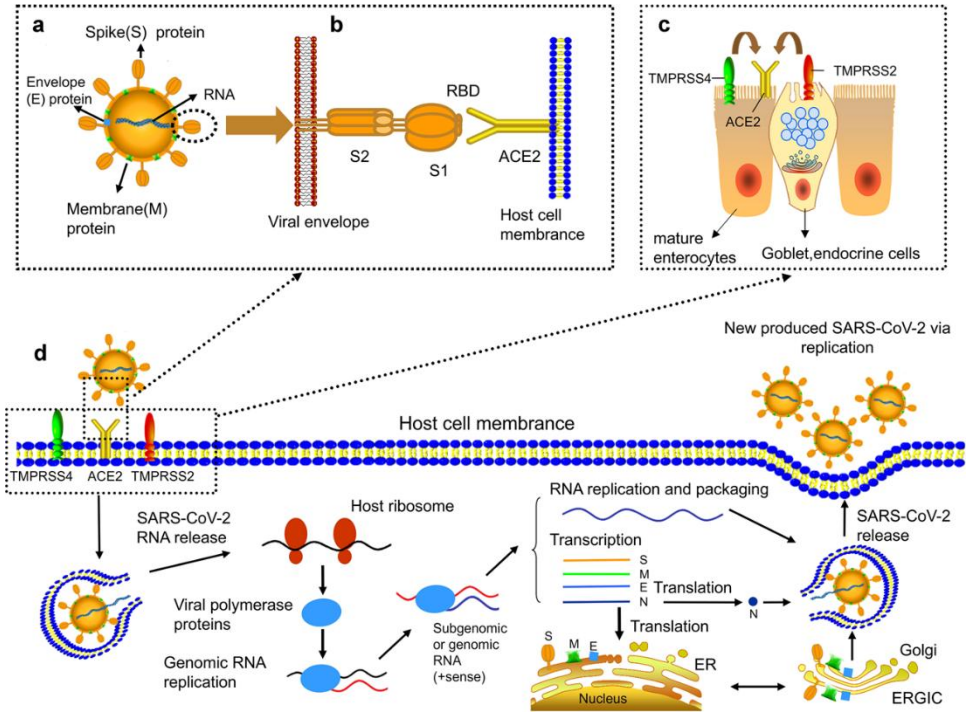

Fig. 3: The life cycle of COVID-19 in intestinal hosts[34]

2.1.3 The effect of COVID-19 on blood coagulation

Another major syndrome related to COVID-19 is the presence of abnormalities in coagulation. Severely infected patients have a significantly higher tendency to thrombosis compared to those mildly infected, and the majority of them showed an increase in the levels of D-dimer and fibrinogen degradation products. This complication is also indicative of the criticalness of the disease and is reported to cause the death of 20 to 30 percent of critically ill patients [35].

As the virus enters the body via ACE2 receptors, it is recognized by the pathogen-associated molecular pattern (PAMP) in the body, which subsequently activates the immune system. The overactivation of the immune system causes the excessive production of white blood cells, which increases the inflammatory factors. Excessive immune system activation also leads to cytokine storms, which then results in microvascular damage, activation of the coagulation system, and inhibition of fibrinolysis and the anticoagulation system [4][36]. Additionally, the cytokine release syndrome (CRS) activates interleukin 6 (IL-6), an inflammatory mediator that stimulates the synthesis of thrombopoietin, fibrinogen, and other clotting factors [37][38].

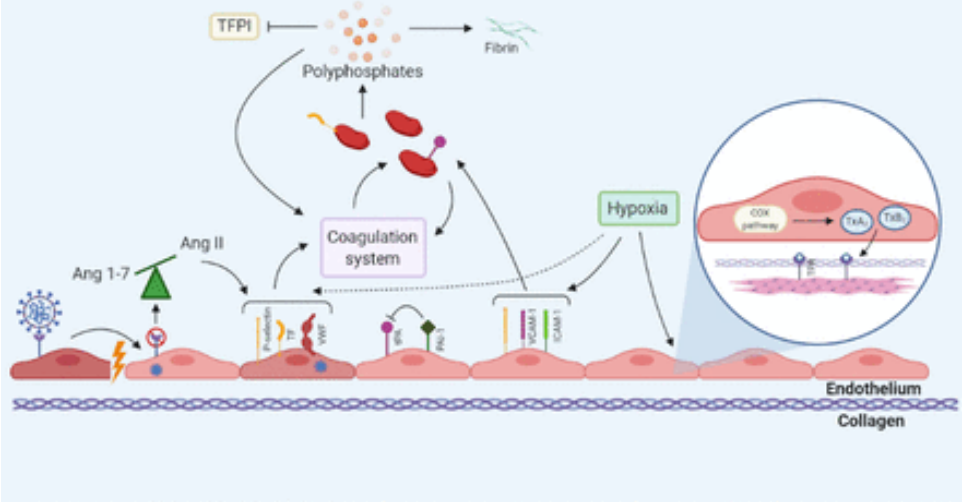

Fig. 4: Endothelial dysfunction caused by COVID-19[39]

2.2. Turmeric as an Alternative Treatment Option to COVID-19 Symptoms

Turmeric, or scientifically *Curcuma longa*, is a perennial plant with wide, oblong leaves and a short stalk. It has branching tubers (rhizomes) that are oblong, ovate, or pyriform. The plant's main active ingredient, curcumin, is one of the most studied phytochemicals. Reports regarding this curcuminoid show positive results in helping reduce inflammation in the gastrointestinal system and on the skin. Curcumin has also been demonstrated to activate other defensive processes in cell systems, including boosting antioxidant enzymes, inhibiting inflammatory processes, and altering signal transmission and transcription factors [40]. Turmeric has shown to be an alternative or adjunct treatment option for COVID-19 due to its antiviral, antipyretic, anti-inflammatory, antiemetic, antioxidant, and inhibitory effects on cytokines and chemokines [41].

The focus of this paper is curcumin's therapeutic effects on the lungs, gastrointestinal tract, and blood coagulation.

2.2.1 Turmeric for the lungs

Growing data from pharmacological studies indicate that curcumin has a role in protecting the lungs from conditions like allergic asthma, acute respiratory distress syndrome, acute lung injury, and chronic obstructive pulmonary disease. Its curative action is centered on preventing and regulating oxidative stress and inflammation [42].

Curcumin's ability to modulate cellular death, inflammation, and antioxidant generation in BaP-induced lung injury in rats is suggested in numerous studies. Notably, the findings point to the need for more research into curcumin or structurally comparable analogs as cytokine and cytokine-regulated gene inhibitors. Curcumin's anti-inflammatory tumor-suppressing efficacy and anti-oxidative properties have been examined previously. As a result, curcumin could be used as a viable therapeutic method for BaP-induced lung injury and other pollution-related illnesses [43].

The anti-inflammatory effect of curcumin involves the regulation of several targets. Nuclear factor-kappa B (NF-B) is a transcription factor modulating gene expression in innate and adaptive immunity, as well as inflammation. The anti-oxidative that is found on the constituent has been demonstrated in vitro and in animal experiments. Additionally, curcumin is also a lipid peroxidation inhibitor and is important in maintaining the action of many antioxidant enzymes such as catalase, superoxide dismutase, and glutathione peroxidase in vitro and in vivo. Subsequently, it activates the NF-E2 related factor (NRF-2), an important antioxidant transcriptional factor [44].

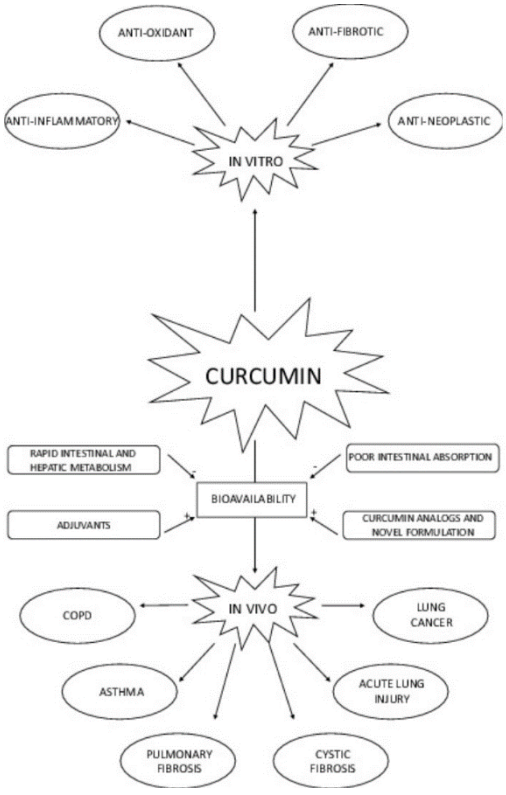

Fig. 5: Therapeutic effects of curcumin in the lungs[44]

2.2.2 Turmeric for the gastrointestinal tract

Numerous claims in ethnomedicine about plants utilized in Indian traditional systems of medicine as gastroprotective agents have been substantiated by scientific investigations conducted over the last three decades. For instance, turmeric has recently been demonstrated to exhibit gastroprotective properties at safe dosages in preclinical investigations [45]. Curcumin, the plant's main curcuminoid and one of the most studied phytochemicals, is frequently reported to reduce inflammatory reactions in the gastrointestinal system because of its ability to scavenge free radicals and chelate compounds [40]. Moreover, due to its higher bioavailability in the gastrointestinal tract, curcumin may decrease the progression of gastrointestinal malignancies such as esophageal, oral, stomach, colon, and intestinal cancers. Curcumin has also been a suggested treatment for liver and other digestive problems such as Crohn's disease, bacterial and parasite infections, irritable bowel syndrome, and colitis [46].

Through scavenging superoxide anion, singlet oxygen, hydroxyl radical, and other oxygen species, curcumin impedes peroxide-induced DNA damage lipid peroxidation. It also regulates various signaling molecules, thereby producing anticarcinogenic and anti-inflammatory effects. Moreover, curcumin hinders protein kinases, prostaglandin synthesis, activation of c-Jun/AP-1, and the expression of cyclooxygenase, an enzyme critical for cell growth, differentiation, and malignant transformation in vitro [47].

Clinical investigations in humans show that orally given curcumin has a limited systemic bioavailability and that curcumin metabolites, not the constituent itself, are found in the plasma or serum [48]. Curcumin is quickly converted to curcumin glucuronide and curcumin sulfate in the colon and liver or reduced to tetrahydrocurcumin, hexahydrocurcumin, and octahydrocurcumin in the liver (as shown in Figure 6). An early clinical study in Taiwan showed that one hour after administration of 4 to 8 grams of curcumin, serum concentrations of the constituent peaked between 0.41 to 1.75 micromoles per liter [49]. Meanwhile, a clinical experiment in the United Kingdom demonstrated that plasma concentration of curcumin, curcumin glucuronide, and curcumin sulfate were at 0.01 M an hour after an oral dosage of 3.6 grams of curcumin [50]. At dosages of less than 3.6 g/day, curcumin and its metabolites were undetected in plasma. There is some indication that curcumin taken orally accumulates in the gastrointestinal tract. In patients orally taking curcumin 3.6 grams one week before surgery, curcumin was identified in normal and malignant colon tissues [51]. However, it was undetected in the liver tissue of patients with colorectal cancer liver metastases following the same oral dosage, implying that oral curcumin administration may not efficiently transfer curcumin to tissues beyond the gastrointestinal system [52].

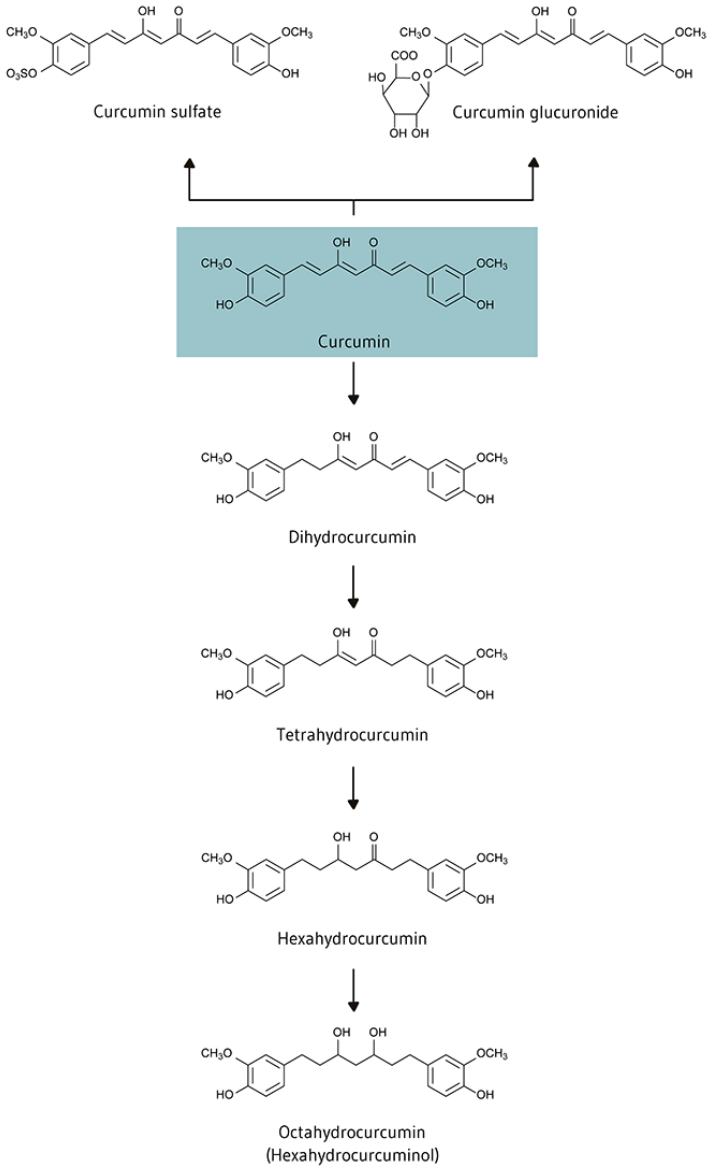

Fig. 6: Curcumin metabolites [53]

The safety and effectiveness of many curcumin formulations are now being investigated in preclinical settings in order to improve curcumin absorption, bioavailability, and tissue-targeted delivery. Several techniques for this include conjugation to peptide carriers, coadministration with piperine, complexation with essential oils, and encapsulation in nanoparticles, liposomes, phytosomes, polymeric micelles, and cyclodextrins [54].

2.2.3 Turmeric for blood coagulation

Another interesting property of turmeric that has gained the attention of the scientific field is its ability to become a blood thinner. In vivo demonstrations revealed that curcumin successfully prolonged prothrombin time (PT) and activated partial thromboplastin time (aPTT) by inhibiting Factor Xa (FXa), a serine protease that cleaves prothrombin to thrombin. These results show that curcumin strongly correlates with many of today's blood thinners [55][56]. Another study showed that the formation of thromboxane B2 was significantly reduced in human blood samples treated with turmeric, demonstrating that turmeric may have the ability to prevent platelet aggregation [57].

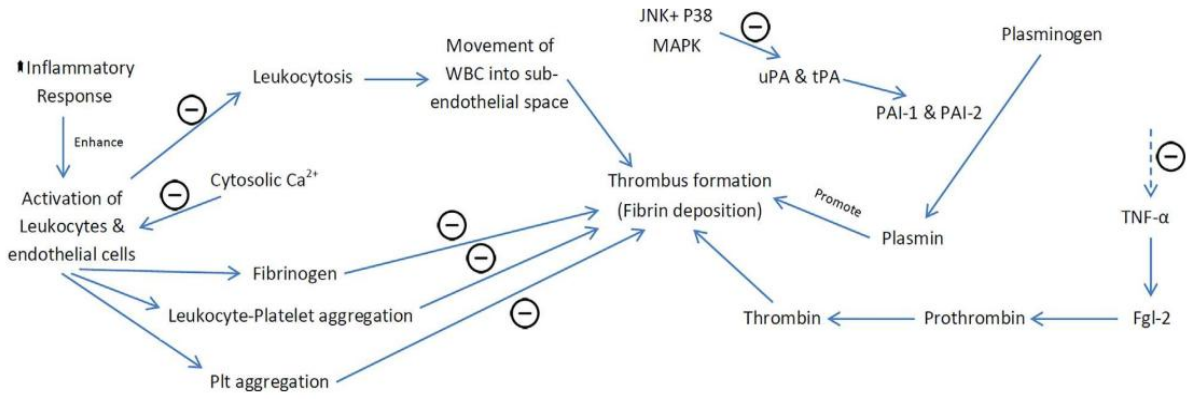

Fig. 7: Mechanism of curcumin's anticoagulant effect [58]

Madhyastha et al. [58] also explained that curcumin promotes cellular migration and fibrinolysis during tissue regenerations. Using plasminogen activator antagonists 1 and 2, it was established that P38 mitogen-activated protein kinase and c-Jun N-terminal kinases (JNK) modulated the urokinase-type plasminogen activator (uPA) transcriptional activation in a dose-dependent method (PAI-1 and PAI-2 and that this resulted in a significant advancement of coagulation factors using curcumin.

The occurrence of hydrophobic groups in curcumin is found to be significant for its anticoagulant activity [55]. Curcumin's anticoagulant effects were superior to those of bisdemethoxycurcumin (BDMC), a curcumin derivative. This demonstrates that curcumin's anticoagulant action was favorably regulated by the methoxy group [59].

3. Discussion

COVID-19 primarily manifests as a respiratory illness with symptoms like cough, dyspnea, and colds. As the virus invades pulmonary cells, it replicates itself and causes inflammation as an immune response, which continues and subsequently causes eventual lung damage. However, because of the virus' mechanism of binding to ACE2 receptors which are generously distributed throughout the body, it affects other major organs. In the gastrointestinal tract, the virus causes manifestations such as diarrhea, nausea, acid reflux, and anorexia. Meanwhile, the virus affects the blood by over-activating the immune system, leading to the excessive synthesis of white blood cells. This results in inflammation and cytokine storms, which cause damage to the microvasculature and activation of the coagulation system. One treatment for the manifestations of COVID-19 backed-up by established evidence from multiple studies is turmeric, or specifically its constituent curcumin. It possesses the ability to regulate cell death and inflammation in the lungs, which suggests that it can help in respiratory symptoms. Curcumin is also found to be bioavailable in the gastrointestinal tract, which means that it may be highly effective in alleviating digestive symptoms. Additionally, the constituent works as an anticoagulant via the inhibition of Factor Xa, a protease responsible for the cleaving of prothrombin to thrombin.

4. Conclusion

After thoroughly explaining the impacts of COVID-19 in the lungs, gastrointestinal tract, and blood coagulation, as well as demonstrating the therapeutic uses of turmeric specific for the aforementioned body systems, it can be concluded the curcumin as a constituent of turmeric has shown therapeutic properties in the various manifestations of COVID-19 mentioned in this study. This alternative treatment for the virus is strengthened by numerous studies and should therefore be considered.

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