Curcumin as Adjuvant Therapy in COVID-19: Friend or Foe?

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Abstract

COVID-19, which is caused by SARS-CoV-2, quickly spreads in many countries and was declared as a pandemic. To date, there is no effective drug that is proven against COVID-19. Curcumin has various beneficial effects, including anti-inflammatory, antioxidant, antimicrobial, and antiviral properties. Curcumin containing herbal drink is famous to boost immune response, and curcumin was shown to bind to viral S1 protein, which is important for viral entry, in an in silico study. Therefore, administration of curcumin containing herbal drink may be beneficial to prevent COVID-19 and cytokine storm in severe form of COVID-19. However, high dose curcumin was showed to increase expression of ACE2 in myocardial fibrosis rat model. Therefore, there is a fear that curcumin may help viral entry into the cell, as ACE2 is the receptor for SARS-CoV-2 entry into cells. However, looking at the dose of curcumin in the herbal drink, it is unlikely that the dose will cause an increase in ACE2. In conclusion, curcumin may be beneficial as adjuvant to other drugs to prevent COVID-19 and cytokine storm in severe COVID-19, but studies are needed to get more robust prove, and to determine the optimal dose and timing of administration.

Keywords: Curcumin; COVID-19; SARS-CoV-2; ACE2; cytokine storm; anti-inflammatory.

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Introduction

Pneumonia cases of unknown origin were reported to the WHO by China Government in 31 December 2019. The cause was identified as a new coronavirus i.e. 2019 novel coronavirus (2019-nCoV) that was named SARS-coronavirus 2 (SARS-CoV-2), while the disease it causes was named coronavirus disease (COVID-19)14. COVID-19 quickly spreads and cases were found in many countries. Therefore, on 11 March, the WHO declared COVID-19 as a pandemic5.

Till to date, there is no proven effective treatment for COVID-19, though dozens of existing compounds were suggested to be tested. However, the WHO has chosen four compounds to be tested in global megatrials as potential drugs against COVID-19 to prevent serious harm and death, namely Remdesivir, Chloroquine and hydroxychloroquine, Ritonavir/lopinavir, and Ritonavir/lopinavir/interferon-beta combination6.

One of the various candidates, which are not chosen to be tested as treatment for COVID-19, is curcumin. Curcumin as adjuvant to antiviral or other viral eliminating drugs might help in combatting COVID-19. Therefore this article discussed the pathogenesis of COVID-19, the role of curcumin in modulating COVID-19 pathogenesis, and prospect of curcumin as prevention of severe COVID-19.

COVID-19 pathogenesis

SARS-CoV-2 is an RNA virus with several membrane bound proteins. The most important protein, which plays a role in COVID-19 pathogenesis, is spike glycoprotein (S protein) that is anchored at viral envelope. Based its sequence, SARS-CoV-2 spike protein contains a receptor binding motif (RBM) in a receptor binding domain (RBD) that binds to a host cell receptor. A study concluded that to enter a cell, host cell serine protease TMPRSS2 is needed for S protein priming, where the S protein is cleaved into S1 and S2. The S1 protein binds ACE2,
which acts as a receptor for SARS-CoV-2 entry into cells\(^7\),\(^8\),\(^9\), and S2 protein facilitates viral and host cell membrane fusion, followed by viral material entry into the host cell and viral replication (Figure 1)\(^10\). ACE2 is a membrane bound enzyme that is found on cell surfaces, such as type 2 alveolar cells of lungs, oral mucosa, especially epithelial cells of the tongue, stratified epithelial cells of oesophagus, columnar epithelial cells of ileum and colon, cholangiocytes of liver, proximal tubule cells of kidney, bladder urothelial cells, and myocardial cells\(^ {11} \).

Further, ACE2, which protect from lung injury, is down regulated by S protein\(^7\). Upon entry and viral replication, various symptoms might develop from very mild to severe. In most cases, the body immune response develops and contained the disease. However, in severe cases, uncontrolled pro-inflammatory cytokine release (cytokine storm) occurs in response to the virus that may lead to multi organ failure and death\(^12\).

**Curcumin and modulation of COVID-19 pathogenesis**

Curcumin (1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione), which is also called diferuloylmethane, is a phytochemical that can be extracted from the rhizome of turmeric (Curcuma longa L. and its related species). Turmeric is usually used as a spice in various kinds of foods and beverages in various countries, especially Asian countries. Moreover, it has been used as medicinal herb for around 4000 years, and has been documented in Ayurveda and Traditional Chinese Medicine to treat various diseases due to its various beneficial effects, including anti-inflammatory, antioxidant, antibacterial, antiviral, anti-mutation, and anticancer properties\(^ {13} \).

Curcumin for treatment is available in various forms, which can be extracted from turmeric and its related species, either alone or in combination with other curcumin like substances, i.e. demethoxycurcumin (DMC) and bidemethoxycurcumin (BDMC) that have similar biological activity as curcumin and together they are known as curcuminoids. Curcuminoids contains curcumin (77%), DMC (17%), and BDMC (3%)\(^ {14} \).

**Curcumin as friend: Prevention COVID-19 and modulation of severe COVID-19**

In Indonesia, an Indonesian scientist has developed a curcumin containing herbal drink, to be used as adjuvant to western medicine\(^ {15} \). The recipe to make the herbal drink is widely available and claimed to boost the immune system. The herbal drink contains various kinds of herbs including 100 g of curcumin rich fresh root of Curcuma Xanthorrhiza\(^ {16,17} \).

When SARS-CoV-2 infects an individual, several factors are responsible to determine development of COVID-19, i.e. viral (viral number and virulence), host (health state, host immune system, nutrition, etc.), and environment factors. When SARS-CoV-2 wins the battle, infection can range from mild to severe. Therefore, the use of curcumin containing herbal drink, which boosts the immune system, might help the body to win the battle against SARS-CoV-2, and thus prevent COVID-19 infection and might be used as prophylactic in health care providers.

Moreover, curcumin was showed to have antiviral property against various kinds of viruses, i.e. zikavirus (ZIKV), chikungunya virus (CHIKV), human immunodeficiency virus (HIV), herpes simplex virus 2 (HSV-2), human papillomavirus (HPV), hepatitis viruses, influenza viruses, etc\(^ {18,19} \). A recent in-silico study showed that curcumin could bind to RBD of S protein\(^ {20} \). Therefore, studies are needed to elucidate whether curcumin really can bind the S protein and therefore prevent SARS-CoV-2 infection, and whether the dose in the curcumin herbal drink is optimal for COVID-19 prevention, thus might be used as prophylactic in health care providers.

In severe form of COVID-19, acute respiratory distress syndrome (ARDS) may occur. The mechanism of ARDS is due to a large amount release of pro-inflammatory cytokine\(^ {22} \). In various conditions with elevated inflammatory cytokines, curcumin was shown to reduce the inflammatory cytokines i.e. tumour necrosis factor-\(\alpha\) (TNF-\(\alpha\)), interleukin-6 (IL-6), IL-1\(\beta\), IL-4, and monocyte chemoattractant protein-1 (MCP-
supplementation 400 mg/day showed significantly lower serum TNF-α and IL-6, but non-significantly lower IL-8 and IL-10 compared to placebo.

Finally, a systematic review and meta-analysis of curcumin effect on superoxide dismutase (SOD), which is an enzyme with antioxidant and anti-inflammatory properties, showed an overall increase in SOD after curcumin supplementation. Curcumin doses, which caused increases in SOD in the studies that were included in the systematic review, were: 1,000 mg/day (500mg curcumin C3 Complex + 5mg piperine, twice a day) (two studies), 1,500 mg/day (500mg curcumin C3 Complex + 5mg piperine, three times a day) (two studies), and 180 mg/day of lipidated curcumin (curcuminoids + soy phosphatidylcholine [lecithin] in 1:2 weight ratio) 25.

Curcumin as Foe: Facilitation of Viral Entry??

A study showed that oral curcumin (Sigma-Aldrich Co) 150 mg/kg body weight (BW)/day increased expression of ACE2 in myocardial fibrosis rat model 26. Therefore, curcumin at a dose of 150 mg/kg BW may help viral entry into the cell, at the early stage of the disease, before the body immune system develops and copes with the disease. Therefore, Curcumin containing herbal drink should be used with caution if it was intended to prevent COVID-19 infection, when the dose of curcumin in the herbal drink reached 150 mg/kg BW (7,500 mg for a subject with 50 kg BW). However, the herbal drink is prepared using 100 g of fresh Curcuma xanthorrhiza 16, 17 that yields around 5 g of dry weight and contains a range of 3.60 – 7.99 % curcumin when planted in various cultivation conditions27. Thus a cup of herbal drink only contains 180 –400 mg of curcumin. It is suggested to take the herbal drink twice a day to boost the immune response, so that the curcumin dose/day is only 360 -800 mg, far below the dose of Pang et al study26 that showed increased ACE2 expression after curcumin oral intake. Moreover, the herbal drink is prepared by boiling the ingredients in water until the water boils 16, 17, 18 while curcumin has a lipophilic nature and is not readily soluble in water at room temperature4, 28 boiling may increase curcumin solubility.
There are also questions, whether the curcumin containing turmeric, which is found in certain food and beverage, is of enough dosage to increase the expression of ACE2, and whether people who consume the curcumin containing food or beverage are more susceptible to contract COVID-19. The amount of turmeric in a dish is approximately 50 g fresh turmeric for 6 servings\textsuperscript{29,30}, and a cup of immune boosting turmeric golden milk is made using a half tea spoon (1 g) of turmeric powder \textsuperscript{31}. The content of curcuminoids in fresh turmeric varies between 3.76-5.05 \%\textsuperscript{32}, 2.9 \%\textsuperscript{33}, and 1.33-1.92 \%\textsuperscript{34} depending on the source of turmeric, isolation and detection method. Therefore the content of curcumin in a dish of six servings is 0.67 – 4.50 g, and the content of curcumin per serving is only 110 –750 mg. Further, curcumin content may vary between various commercially available powders, but a study showed that pure turmeric powder contained 3.14\% curcumin\textsuperscript{35}. Therefore, a cup of turmeric golden milk, which uses 1 g of turmeric powder \textsuperscript{31}, contains only 30 mg of curcumin. In summary, curcumin content in food and beverage is far below the dose of Pang et al study\textsuperscript{26} that showed increased ACE2 expression after curcumin oral intake.

Therefore, it is supposed that curcumin content in Indonesian immune boosting herbal drink or various curcumin containing food and beverage may not facilitate SARS-CoV-2 entry into the cells, or increase susceptibility to COVID-19. However, to be sure, studies are needed to know whether lower doses than those used by Pang et al\textsuperscript{26} can cause increase in ACE2 expression, and the highest dose that is still safe.

**Prospect of curcumin as prevention of both COVID-19 infection and its severe manifestation**

Some clinical trials showed that doses between 4000 and 8000 mg/day and up to 12,000 mg/day had good tolerability and safety profile. Therefore, the use of curcumin and curcuminoids has been approved by the US Food and Drug Administration (US-FDA) and is regarded as safe. The Joint United Nations and World Health Organization Expert Committee on Food Additives (JECFA)\textsuperscript{36} and European Food Safety Authority (EFSA)\textsuperscript{37} reports had set an Allowable Daily Intake (ADI) value of curcumin to be 0–3 mg/kg BW. A high intake may result in several negative side effects, as several studies reported diarrhea, headache, rash and yellow stool after consuming 500 – 12,000 mg curcumin/day in a dose response study, and nausea, diarrhea, increased serum alkaline phosphatase and lactate dehydrogenase after consuming 450 to 3,600 mg curcumin /day for one to four months\textsuperscript{13}.

To prevent COVID-19, curcumin containing medicinal product (herbal drink) should contain a curcumin dose of less than 7,500 mg/day, to prevent increased expression of ACE2. Therefore, Indonesian curcumin containing herbal drink may be a suitable candidate, as it contains a low dose curcumin. However, in vitro and in vivo studies are needed to prove whether the herbal drink indeed can boost the immune system, and has an antiviral activity against SARS-CoV-2 to prevent SARS-CoV-2 infection. As curcumin content may vary according to various factors, i.e. geographical factors of cultivating region\textsuperscript{32}, soil factors, genus diversity\textsuperscript{35}, the use and type of fertilizers \textsuperscript{32}, developmental stage and time of harvest \textsuperscript{38}, standardization of optimal curcumin dose needs to be conducted.

To prevent cytokine storm, curcumin dose that exerts anti-inflammatory response is needed. Various studies showed that various doses below 7,500 mg/day were effective to significantly lower various cytokine levels, or boost anti-inflammatory responses in various conditions\textsuperscript{13,21-25}.

Therefore, to be used as adjuvant for prevention and modulation of cytokine storm in severe COVID-19, further studies are needed to determine the optimal dose, which may have anti-inflammatory effect, and timing of administration. As the dose to exert anti-inflammatory response may be higher than those needed for COVID-19 prevention, studies on special formulation that can increase curcumin bioavailability may be needed.

**Conclusions**

Curcumin may be beneficial to prevent COVID-19 infection by boosting the immune system, and to prevent and modulate cytokine storm in severe form of COVID-19. However, studies are needed to determine the optimal dose, formulation, and timing of administration for both prevention of infection and severe COVID-19.


