

# COKELAT HITAM SEBAGAI MAKANAN KAYA NITRIC OXIDE UNTUK MENANGGULANGI COVID-19: SYSTEMATIC REVIEW



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## Abstrak

Coronavirus Disease 19 (COVID-19) merupakan penyakit mematikan yang dapat membunuh ribuan orang di dunia. Namun, tidak banyak peneliti yang menyadari bahwa kandungan NO dapat membunuh virus COVID-19. Metode penelitian ini adalah desain penelitian menggunakan metode retrospektif, prospektif dan tinjauan sistematis. Pencarian sumber referensi dimulai pada 10 Maret - 01 Juni 2021, menggunakan beberapa database online: 1) Pubmed, 2) Science Direct, 3) Google Scholar. Kata kunci yang digunakan dalam pencarian istilah: COVID-19, novel Coronavirus, SARS-CoV-2, nitric oxide (NO), coklat hitam, macrophages dan termasuk dalam jurnal yang terakreditasi. Penelitian ini mencari daftar referensi dari penelitian yang meliputi 103 penelitian yang diambil melalui pencarian. Sebanyak 63 pasal dalam pembersihan, dan ada 8 pasal yang masuk dalam pembahasan. Hasil tinjauan ini memberikan bukti bahwa COVID-19 dapat dilemahkan dan dimatikan oleh kandungan NO yang dihasilkan oleh makrofag dan disuplai dengan konten NO yang dimodulasi oleh coklat hitam. modulasi makanan kaya NO seperti coklat hitam dapat efektif dengan efek protektifnya sebagai bentuk pencegahan dari paparan COVID-19. NO juga dapat menyembuhkan beberapa penyakit seperti tekanan darah tinggi, diabetes, penyakit kardiovaskular dan beberapa infeksi saluran pernapasan.

**Kata kunci:** Covid-19, coklat hitam, modulasi, nitric oxide, pandemic

## DARK CHOCOLATE AS A FOOD RICH IN NITRIC OXIDE TO PREVENTING FROM COVID-19: A SYSTEMATIC REVIEW

## Abstract

Coronavirus 19 is a deadly disease that can kill thousands of people worldwide. However, not many researchers know that NO content can kill the COVID-19 virus. This research method is study design used retrospective methods, prospective and a systematic review. Search for reference sources began on March 10th - June 1st, 2021, using several online databases: 1) Pubmed, 2) Science Direct, 3) Google Scholar. Keywords used in the search term: COVID-19, Novel Coronavirus, SARS-CoV, Nitric Oxide, Dark Chocolate, Macrophages and included in journals accredited. This study looked for a list of references from the study, including 103 studies taken through the search. There are 63 articles in cleaning, and eight articles are included in the discussion. This review shows that COVID-19 can be attenuated and killed by the NO content produced by macrophages and supplied with NO content modulated by dark chocolate. Modulating NO-rich foods such as dark chocolate can effectively kill COVID-19. NO can also cure several diseases such as high blood pressure, diabetes, cardiovascular disease, and some respiratory infections.

**Keywords:** Covid-19, dark chocolate, modulation, nitric oxide, pandemic

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## Introduction

Coronaviruses are a large family of viruses. Some coronaviruses cause cold-like illnesses in people, while others cause diseases in certain animals, such as cattle, camels, and bats. Some coronaviruses, such as canine and feline coronaviruses, infect only animals and do not infect people. If humans and animals are exposed to this type of virus, it will infect the respiratory system. Symptoms that appear include flu that happened in middle east respiratory syndrome (MERS), severe acute respiratory syndrome (SARS), and other acute infections of the respiratory system<sup>(1-4)</sup>. COVID-19 was first detected in Wuhan, China, in December 2019, caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Therefore, this disease is called Coronavirus Disease-2019 (COVID-19)<sup>(4-7)</sup>.

The development of COVID-19 in Indonesia on April 19th, 2020, with 6,248 cases as details of 5,082 treated, 535 mortality cases, and 631 cured, classified as still very high. From these data, it can be seen that there was an increase from April 18th, 2020, to 5,293, which increased 325 cases higher. At the end of June 10th, 2020, the Indonesian Ministry of Health data showed an increase in the incidence of COVID-19 that reached above 100%<sup>(8)</sup>.

The high number of cases of COVID-19 patients is increasing, causing greater concerns. The virus quickly spreads in various ways, including when the patient sneezes, the virus can live for 3 hours in the air, and when the droplet (items that can make this virus survive and develop) this virus can live for 3-7 days in plastic, iron, and steel. Therefore, the spread will be faster when many crowds or positive sufferers of COVID-19 are still doing everyday activities<sup>(1,7,9,10)</sup>.

COVID-19 causes damage to internal organs, so clinical symptoms will appear in patients. Clinical symptoms that arise such as mild symptoms: cough, runny nose, sore throat, fatigue, indigestion, and skin rashes, and severe symptoms: acute respiratory distress syndrome, coughing up blood, severe headaches, and high fever<sup>(1,3,11)</sup>. Everyone has the possibility of being infected with this virus, depending on how the immune system

that works against this virus because COVID-19 can attack the human immune function and become a virulent virus that is deadly to thousands of people in the world<sup>(4,12-15)</sup>.

All types of parasites can naturally be killed using Nitric Oxide (NO) by macrophages when entering the body, including the COVID-19 virus (16-19). NO, produced by macrophages, can be found in organs such as the lungs and skin (17,18,20). NO is a vital signal delivery molecule between cells that have been shown to have an inhibitory effect on several viral infections (14,21,22). Naturally, the human body has macrophages that can kill parasites in our body. NO produced by alveolar macrophages helps host defense against infection by inducing anti-mycobacterial activity by TNF- $\alpha$  and IFN- $\gamma$ <sup>(17,23,24)</sup>.

NO produced by macrophages cannot kill COVID-19; this is because the amount of this virus is too substantial for NO produced by macrophages. Thus, it requires NO modulation through foods containing NO to enhance the patient's immune system and kill COVID-19<sup>(6,24-26)</sup>. Food sources that have high NO such as dark chocolate, avocado, and pomegranate, are effectively used to increase the patient's immunity<sup>(27-30)</sup>.

Consumption of dark chocolate can indirectly improve health status because it can induce NO, which causes vasodilation and inhibits cyclooxygenase (COX)-2, C reactive protein (CRP), and atherogenesis. Then polyphenols from chocolate can also bring up antioxidant effects, thereby increasing neurological function and preventing premature aging. In addition, the synthesis of polyphenols in chocolate also provides benefits through the activation of endothelial NO synthase (eNOS), inhibiting the activation of NADPH and others, which ultimately can improve health status<sup>(6,29,31-33)</sup>.

## Methods

Search for reference sources or literature began on March 10th - June 01st, 2021, using several online databases: 1) Pubmed, 2) Science Direct, 3) Google Scholar. Keywords used in the search term: COVID-19, Novel Coronavirus, SARS-CoV, Nitric Oxide, Dark Chocolate, Macrophages and

included in journals accredited by publications. The studies were included if 1) human studies; 2) published in English or Indonesian. This study looked for a list of references from the study, including 103 studies taken through the search. A total of 63 articles in cleaning, and there are eight articles included in the discussion, about the study design used retrospective methods, prospective, and a systematic review. A systematic review is a review of a formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant research and collect and analyze data from the studies included in the review<sup>(7)</sup>.

### Results and Discussion

Darwish et al. (2012) investigated the inhalation of nitric oxide (iNO), which influences the development of influenza type A viruses. Based on the results of their study, it shows that NO has antiviral against influenza type A viruses<sup>(34-37)</sup>. Research conducted by<sup>(38)</sup> in a hospital using 37 seropositive patients and 40 control groups to test differences in serum Malondialdehyde (MDA), Glutathione (GSH), and NO levels. The IgG result from the patient group was  $1,013.0 \pm 543.8$  in optical density (mean  $\pm$  SD). Statistically significant differences were found between patients and control groups regarding MDA, GSH, and NO levels. In conclusion, a decrease in GSH activity was detected, while MDA and NO levels increased significantly. The use of antioxidant vitamins, in addition to the treatment of parasites, has proven to be beneficial. High infection vs. control ratio of MDA and NO levels may show events as a mechanism of tissue damage in cases of chronic toxoplasmosis. In addition, it is recommended that the patient's MDA, GSH, and NO levels should be evaluated in toxoplasmosis<sup>(36,38-40)</sup>.

Ren (2013) conducted a study in a housing group, with a sample of 36 men aged 55 to 62 years randomly. Their test runs for 12 weeks, 4 times per week, 45 minutes for each time, the target heart rate is 100 ~ 110 beats/minute (group L), 110 ~ 120 beats / minute (group M), 120 ~ 130 beats / minute (group H). With fasting at night, all venous blood samples are taken by 4ml before

and after exercise. The conclusion is recommended that the more appropriate exercise intensity is 100-120 beats/minute for the elderly during fitness training, and specifically 110-120 beats/minute. Such intensity training can increase NO in vivo content, thereby effectively preventing cardiovascular disease<sup>(41)</sup>.

A study in Iran was conducted by Ayoobi et al. (2017) in Iran among 44 diabetes patients using dark chocolate to find the association between NO levels and heart health. The results showed that dark chocolate consumption is proven to increase NO levels, which is good for the heart health of people with diabetes<sup>(28)</sup>. This finding is similar to the research conducted by Innes et al. (2003) among 30 random volunteers using 100 g of dark chocolate. The results showed that dark chocolate has a high NO level and plays a role in preventing cardiovascular disease<sup>(42)</sup>.

Figure 1. COVID-19 Prevalence, Republic of Indonesia Ministry of Health 2020 data <https://infinemerging.kemkes.go.id/>.



Lei et al. (2020) stated that NO supplementation could improve oxygenation and survival of SARS-CoV-2 patients. Supplementation is done by inhalation of Nitric Oxide (iNO). Besides, NO donors can also increase the survival rate of cells infected with SARS-CoV-2; it shows the direct effect as an antiviral. Most COVID-19 patients show effectiveness in the use of iNO therapy. However, NO treatment must be carried out in a controlled manner with regular doses adjusted to the patient's condition. The iNO dose during the therapy process will gradually be reduced when the patient's condition improves according to the protocol, which aims to stop treatment progressively because the sudden cessation of iNO therapy can cause oxidation disorders and acute heart

failure<sup>(10)</sup>.

A study conducted on 32 patients in one hospital mentioned that the serum NO level between the treatment and control groups was significantly different from  $7.70 \pm 3.84$  vs.  $1.92 (-0.79 + 17.78)$  ( $p = 0.001$ ) (Sudarma et al., 2011). Both groups experienced a decrease in systolic and diastolic blood pressure. Systolic blood pressure differed significantly between groups after treatment  $120.64 \pm 8.47$  vs  $131.19 \pm 7.45$  ( $p = 0.001$ ), while diastolic blood pressure was not significant  $74.14 \pm 6.30$  vs  $77.44 \pm 10.29$  ( $p = 0.308$ ). It can be concluded that in prehypertensive subjects, dark chocolate 30 g/day increases serum NO levels and decreases systolic blood pressure after 15 days of treatment<sup>(27)</sup>.

### Conclusions

COVID-19 is a disease that infects the respiratory tract (respiratory tract infection) such as flu, MERS, SARS or other acute respiratory syndromes. NO is an antiviral source that can fight and kill viruses in the body. NO is produced biologically by small amounts of macrophages. NO in the body cannot prevent COVID-19 because it is too strong. Thus, it requires additional NO from outside the body. Dark chocolate is a food that has a very high NO content that can be used to kill COVID-19 that enters the body. Therefore, modulation of NO-rich foods such as dark chocolate can effectively kill COVID-19. NO can also cure several diseases such as high blood pressure, diabetes, cardiovascular disease, and respiratory infections. However, this study requires further research so that dosing results in patients with COVID-19 or the general public can be following average doses.

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