



The Effect of Nanogold-Nanosilver to Increase the Immunity of People Affected by COVID-19 with Hypertension Comorbidities

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ABSTRACT: The SARS-CoV-2/Covid-19 Coronavirus is currently endemic throughout the world. The comorbidities of Covid-19 with the highest percentage reaching 50.5% are hypertension. Hypertension included in Non-Communicable Diseases (NCD) is generally chronic. It can reduce the sufferer's immune system gradually and is very susceptible to infections, including those caused by viral infections, one of which is the SARS-CoV-2 virus or commonly called COVID-19. Therefore, patients with NCD, especially hypertension, are encouraged to increase immunity and body immunity to avoid virus infection. Currently, nanoparticles, especially Nanogold and Nanosilver, are taking place very rapidly in the health sector because gold and silver nanoparticles have various benefits such as antioxidants, antivirals, and antibacterials. After being proven effective in dealing with leprosy patients in Surabaya, especially in terms of increasing immunity. Now Nanogold-Nanosilver was developed with the hope to help relieve Covid-19 sufferers through increasing the body's immune system because if the body's immune system decreases, the virus will quickly enter the body. In this study, Nanogold and Nanosilver were developed into a health water drink that volunteers can drink every day. Volunteers are people affected by Covid-19 in the Karanganyar area of Surabaya. This study uses a *one-group pretest-posttest design*. The data collection is carried out through direct observation and interviews with people affected by Covid-19 regularly every week. Then the data analysed using a *paired T-test* on the SPSS application. And obtained a *P-value* of 0.000, which means that there is an effect of nanogold-nanosilver for increase body immunity.

KEYWORDS: COVID-19, Hypertension, Nanogold, Nanosilver, Immunity

1. INTRODUCTION

In early 2020, the world was shocked by the outbreak of a new virus, namely SARS-Cov-2, and the disease is called Coronavirus disease 2019 (COVID-19). This virus was detected at the end of December 2020 and is known to have originated from Wuhan, China. This virus is the seventh type of Coronavirus discovered by humans. Genetically, COVID-19 is similar to Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS). This COVID-19 was also found in bats, which influence the onset of this disease [1]. SARS-CoV-2 is thought to have originated in bats because it has an 89-96% nucleotide similarity to the bat coronavirus. The same case with SARS and MERS is suspected that SARS-CoV-2 moved from bats to an intermediate host (possibly the pangolin, with 91% nucleotide similarity) and then moved to humans [2].

The SARS-CoV-2 virus spreads predominantly through respiratory droplets produced when sneezing or coughing and can also indirectly through contaminated objects or surfaces [3]. *Coronavirus* or Severe Acute Respiratory Syndrome Coronavirus 2, known as SARS-CoV-2, attacks the respiratory system and can cause death. Therefore, people with comorbidities are very vulnerable to being exposed to the virus during the COVID-19 pandemic. Some of the comorbidities are Diabetes Mellitus, heart disease, and hypertension [4].

Hypertension or commonly known as high blood pressure is a condition in which a person experiences an increase in blood pressure above normal which can result in morbidity (morbidity) and death (mortality) [5]. Hypertension increases systolic blood pressure above the normal pressure is more than 140 mm Hg and diastolic blood pressure of more than 90 mm Hg. Systolic is the blood pressure when the heart pumps the blood into the arteries (when the heart contracts). Diastolic is the blood pressure when the heart expands or relaxes [6].

Based on data of Covid-19 patients in Indonesia, hypertension is the comorbidities that suffered the most. Along with the easily infectious capacity of the virus, mortality rates have been reported to range from 1% to >5%. Furthermore, it has been reported that patients with COVID-19 and hypertension may have an increased risk for a more adverse outcome [7]. Some studies even said

that groups of patients with hypertension and cardiovascular disease have a tendency to experience severe illness and death when infected with COVID-19 [8].

It's proven that based on data compiled by the Indonesia COVID-19 Task Force as of October 13, 2020, the total confirmed cases of COVID-19, 1.488 patients were confirmed to have comorbidities. Data from comorbidities, hypertension data, is about 12.6%. From 406 patients who died from COVID-19 infection, the total proportion of hypertension was 39.7% for self-reported hypertension. In the 406 patients who died because of COVID-19 infection, the overall proportion of hypertension was 39.7%. However, 81% of patients who died were >60 years old [1].

SARS-CoV-2 can make worsen the condition of people with hypertension. SARS-CoV-2 that attacks ACE2 can eliminate the role of ACE2 in the RAAS system. The Renin-Angiotensin-Aldosterone System (RAAS) is an essential regulator of blood volume and systemic vascular resistance. ACE2 which less effectively inhibits the formation of angiotensin (1-7), is one of the compounds in the feedback system of the RAAS. This inhibition of ACE2 can also cause cumulation of angiotensin II, which has a vasoconstrictive effect [9].

Started from Titik's research to treat leprosy patients in Surabaya in 2017, it is proven that Nanogold can increase the immunity of leprosy sufferers [10]. After being proven effective in dealing with leprosy patients in Surabaya, especially for increasing body immunity. Now the Nanogold-Nanosilver research is being developed with the expectation of helping Covid-19 patients to increase the body's immune system.

Some of the nanoparticles often used in the health sector are gold nanoparticles (Nanogold) and silver nanoparticles (Nanosilver) [11]. Nanogold has activity as an antiviral and antioxidant; Nanogold is a synthetic antioxidant with no carcinogenic effect [12]. Antioxidants are very important in reducing the effects of free radicals which related to degenerative diseases such as high blood pressure [13]. Nanosilver is antibacterial, antifungal, and antiviral because silver ions are highly toxic to bacterial cells, viruses, and eukaryotic microorganisms [13]. Nanosilver also functions as a catalyst for the immune system to eradicate viruses, pathogens, and bacteria in the human body [11].

With a combination of Nanogold and Nanosilver which are strong antigens, antimicrobials, and antivirals. Health water with nanogold-nanosilver is expected to increase immunity to stop the Coronavirus replica, including Covid -19. The volunteers are people in the Gunung Anyar Surabaya who have been affected by Covid-19.

2. MATERIALS AND METHODS

2.1 MATERIAL

The material that used in this research is health water which contains nanogold and nanosilver nanoparticles. The material that is used to synthesise Nanogold is HAuCl_4 , and Nanosilver used AgNO_3 . Both Nanogold and Nanosilver as a reducing material that sodium citrate is needed. For equipment, use a 20-litre panic, stirrer, spoon, and measuring cup. A gas stove is also needed. After the Nanogold and Nanosilver materials were produced, each 20 Ppm then diluted to 2 Ppm. The ratio of Nanogold and Nanosilver is 4:1 and put in a 1000 ml size of the bottle.



Figure 1. Nanogold-Nanosilver health water

2.2 METHODS

This research use pre-experimental with *one group pretest-posttest* design type of research. Pre-experimental design is an experimental activity that aims to determine a symptom or effect that arises as a result of specific treatments. The sampling technique



in this research is consecutive sampling, which is a sampling technique that sets a subject who fulfilled the research criteria to be included in the research for a certain period of time, so it can fulfil the required sample. Data collection techniques are carried out through observation, documentation, and interviews.

First, the researchers interviewed respondents' blood pressure before giving nanogold-nanosilver health water. Then, after the respondents drank the health water regularly for a week the next week, researchers measured the respondent's blood pressure again.

Respondents were people with hypertension who were affected by Covid-19 in the Gunungayar, Surabaya. Nanogold-Nanosilver healthy water is distributed regularly to respondents once a week. And every distribution of healthy water, interviews were also held to record medical notes. Respondents were asked to consume health water products and drink regularly every day. The effects of Nanogold and Nanosilver have been tested and clinically proven safe for consumption because it is non-toxic [14].

Medical record interviews were held from the beginning of August until September 2020 for five weeks every Friday. All team members consisting of a lecturer assisted by two students distributed water to the community/respondents. We also did an interview and took note of medical records, and analysed it. There are various kinds of diseases that people complain about, but we focus more on hypertension. The progress of the respondent's health condition is shown by changes of indicators that were getting better. The indicator is a high blood pressure getting closer to the normal blood pressure, ranging from 90/60 mm Hg to 120/80 mm Hg [15].

Then the results of the research were tested with a *paired sample t-test* to find out that has differences or not in observations. This statistical test was run using SPSS software.

3. RESULTS AND DISCUSSION

3.1 RESULTS

Table 1. General Characteristics of Respondents.

Characteristics	n	Percentage(%)
Gender		
Male	9	30
Female	21	70
Total	30	100
Age		
51-60	15	50
61-70	12	40
71-80	3	10
Total	30	100

Based on the data in **Table 1.** shows that the largest number of respondents who participated in the research were female, with 21 people or about 70% and only nine male or 30%. For the vulnerable age population, the highest number of samples is the age group of 51-60 years there are 15 people or 50%, and the age group 61-70 is 12 people or 40%, and the smallest sample size is the age group 71-80 years or 10% of the total number of samples from all existing samples.

Table 2. The average blood pressure of respondents before and after drinking health water

Blood pressure	Measurement result (mean ± Std deviation)		
	Before	After	Pvalue
Systolic (Before-After)	151,75 ± 12,9109	135,15 ± 11,4804	0,000
Diastolic (Before-After)	87,36 ± 7,2644	75,67 ± 6,0496	0,000



Based on the data in **Table 2**, shows the average results of blood pressure measurements before and after consuming health water with a combination of Nanogold and Nanosilver on it, the results showed that the average blood pressure value of 30 respondents before treatment was 151.75/87.36 mmHg, and in the fifth week after treatment (drink the health water), the average blood pressure decreased to 135.15/75, 67 mm Hg.

If the P -value > 0.05 , it means that there is no significant difference, while if $P < 0.05$, it means that there is a significant difference. The value of 0.05 itself represents a 5% deviation from the normal distribution. And the results of *paired t-test* in table 2, the P -value of the results of systolic and diastolic blood pressure, both 0.000. In other words, health water with a combination of Nanogold and Nanosilver effectively reduces the systolic and diastolic blood pressure of respondents with hypertension through increasing immunity. Moreover, based on data gained from interviews with volunteers, they said that after regularly consuming Nanogold-Nanosilver health water, the symptoms of hypertension such as dizziness, headache, and vertigo slowly decreased. The decreasing of the average high blood pressure and the disappearance of the symptoms indicate a health improvement of the volunteers by increasing the body's immunity.

3.2 DISCUSSION

The relation between hypertension and COVID-19

Based on data compiled by the Indonesia COVID-19 Task Force as of October 13, 2020, of the total confirmed cases of COVID-19, 1.488 patients were indicated to have comorbidities. The highest percentage of it is hypertension with 50.5%. Meanwhile, from the 1.488 cases of patients who died, 13.2% of them had hypertension. And for East Java, until October 2, 2020, patients who died from COVID-19 reached 3.240 people, 91.9% of COVID-19 death cases in East Java followed by comorbidities, with details of hypertension comorbid reach 23%.

Coronavirus disease 2019 (Covid-19) is a systemic disease caused by Corona Virus 2 (SARS-Cov2), which attacks the respiratory system[16]. Comorbidities that suffered by COVID-19 patients are the reason for the highest cases of death due to Covid. One of the comorbidities that can make Covid-19 worsen is hypertension. Hypertension is a non-communicable disease (NCD); it happens when systolic blood pressure increases 140 mm Hg and diastolic blood pressure 90 mm Hg [4].

Patients with Non-Communicable Diseases (NCD), especially hypertension, have so many cases in Indonesia (34.1% prevalence based on RISKESDAS 2018), including one of the groups susceptible to being infected with COVID-19. In addition, several case studies claimed that patients with hypertension and cardiovascular disease also have a tendency to feel severe illness and even death if infected with COVID-19/SARS-CoV-2 [8].

SARS-CoV-2 viruses, such as SARS-CoV and MERS-CoV, are members of the group-coronavirus subgroup. The genome sequences of SARS-CoV-2 and SARS have a similarity of about 79%, but because of the similarity in the receptor-binding domain (RBD) in the S-protein, several analyses have revealed that SARS-CoV-2 uses angiotensin-converting enzyme 2 (ACE2) as a receptor, it like SARS-CoV. The SARS-CoV-2 S-protein directly binds with the ACE2 surface, facilitating viral entry and replication [9].

SARS-CoV-2 can make the condition of people with hypertension worsen. SARS-CoV-2 that attacks ACE2 can eliminate the role of ACE2 in the RAAS system. The Renin-Angiotensin-Aldosterone System (RAAS) is an essential regulator of blood volume and systemic vascular resistance. The reduced effectiveness of ACE2 can inhibit the formation of angiotensin (1-7), which is one of the compounds in the feedback system from RAAS. Inhibition of ACE2 caused angiotensin II to increase which has a vasoconstrictive effect. It caused homeostasis in the blood pressure system did not work and makes blood pressure conditions keep in high pressure or commonly called hypertension [9].

Hypertension which is included in Non-Communicable Diseases (NCD), is generally chronic it can make the sufferer's immune system drop gradually and is very susceptible to infections, including those caused by a virus infection, one of them is the SARS-CoV-2 virus or commonly called COVID-19. Because of it Non-Communicable Diseases (NCD) sufferers are encouraged to increase their immunity and immune system so it can make not easy to be infected by the virus[17].

Also, based on data gained from interviews after regularly consuming Nanogold-Nanosilver health water, the symptoms of hypertension such as dizziness, headache, vertigo, etc., slowly decreased. The decreasing of the average high blood pressure and the disappearance of the symptoms indicate a health improvement of the volunteers by increasing the body's immunity.



The relation between Covid-19 and immunity

Covid-19 cases in Indonesia as of June are currently increasing again; the last update was on June 19, 2021; according to official data from covid19.go.id, active cases of covid-19 reached 1,976,172 confirmed positive of covid-19. One reason why the number of Covid cases increases because people are starting to slack off to comply with all health protocols, like carelessly taking off masks or even not wearing masks, not keeping hand hygiene, then crowding around with many people.

According to Prof. Iris, the immune system can be increased by organising the body's immune system by using immunostimulant. In the immune system, some immunostimulant work in activating various elements and different mechanisms. For example, the function of immunostimulant can increase the body's natural defences to avoid various virus and bacterial infections and other diseases that can reduce or suppress the immune system. In addition, immunostimulants function in helping the immune system work by stimulating the formation of various immune cells that have an essential role in increasing the formation of antibodies [18].

A strong immune system plays a vital role against viral infections. When entering the body, Coronavirus will stick to the cell walls of the respiratory tract and lungs and then step in to cause an infection. First, the immune system will detect this process. Next, the immune system will react by sending white blood cells to build antibodies that will work against the virus. Therefore, it is very important to strengthen the body's immune system so that the body itself can protect against the Coronavirus.

The effectiveness of Nanogold and Nanosilver to increase immunity

A. Nanogold

Antioxidant

Nanogold is a synthetic antioxidant that has no carcinogenic effect [12]. Antioxidants are compounds that can remove, clean, or combine the effects of reactive oxygen species. The role of antioxidants is very important to reduce the effects of free radicals closely related to degenerative diseases like high blood pressure, coronary heart disease, diabetes, and cancer based on biochemical processes in the body [13].

Antivirus

Nanogold has activity as an antiviral. Nanogold can destroy the RNA replica process of a virus because the replica process is not formed, so it automatically does not produce the next generation of viruses because the RNA or DNA replica system has ruined the parent. So Nanogold can regenerate or stimulate damaged cells to grow back to establish a healthier cell network with better immunity. In addition, Nanogold can increase the immune system by building complexes with glutathione in cells [19].

Antigen/Antibody

In an experiment tested on rabbits, 5 mL of gold nanoparticle was injected intravenously, and then after 2 hours, there was a sizeable increase in total leukocytes in 1 mL of blood [20]. In this case, gold nanoparticles used as antigen carriers have been shown to stimulate the phagocytic activity of macrophages and affect lymphocytes' functioning, which is responsible for the immune-modulating effect [21]. The effect of gold nanoparticles on lymphocyte performance was showed by a tenfold increase in proliferation; this fact indicates that Nanogold acts directly to kill the pathogens. In the process, gold nanoparticle was conjugated with peptides then enter the macrophage cytoplasm. After that, the conjugate interacted with the TLR-4 receptor of macrophage, and Nanogold penetrates into the cell, which is accompanied by the secretion of inflammatory cytokines-TNF, IL-1 β , IL-6, and TNF [21]. Nanogold also can increase the immune system at the cellular level by building a complex with glutathione in cells (Ji-Ae, P et al., 2008) [19].

B. Nanosilver

Antibacterial

Nanosilver has antibacterial, antifungal, and antiviral properties because silver ions are highly toxic to bacterial cells, viruses, and eukaryotic microorganisms. Nanosilver is a potent antibacterial due to chemically reactive and easily ionised also the antimicrobial ability of Nanosilver to kill all pathogenic microorganisms, and it has been reported that no microbe that resistant to silver [22]. Nanosilver is an antibacterial that kills gram-positive and gram-negative bacteria. **The antibacterial mechanism** of AgNPs is reached because silver ions are ceaselessly released it can cause bacterial death. AgNPs attach to cell membranes and attack bacteria. Bacterial cell membranes have many phosphorus and sulfur-containing proteins. AgNPs interact with proteins and



DNA in bacterial cells. After AgNPs enter the bacterial cell, it creates a low molecular weight area in the middle of the bacteria. AgNPs interact with ribosomes which can cause disassembly and denaturation of the cytoplasm and inactivation of various enzymes, disrupting the respiratory chain and cell division, which can cause microbial cell death [23].

The antibacterial ability of Nanosilver is affected by the physical characteristics of the Nanomaterial like size, shape, and surface properties. In addition, the ratio of surface area to volume increases with the smaller nanosilver particle size, the stronger the antibacterial ability [24].

Antivirus

Nanosilver has been proven to be a promising antimicrobial and has been considered an option for antiviral treatment. In addition, the literature reviewed on antiviral activity showed that Nanosilver could inhibit viral replication of viruses, such as HIV-1, hepatitis B virus, respiratory syncytial virus, herpes simplex virus type 1, and monkeypox virus [25]. The mechanism is that AgNP binds to the glycoprotein (S) spike membrane through disulfide bonds due to chemical affinity for sulfur. This interaction inhibits the internalisation of the virus in the cells by inhibiting the interaction between glycoproteins and their specific receptors. Absorption of AgNPs cells occurs through the process of endocytosis and macropinocytosis. Once inside the cell, AgNPs can inhibit viral replication [26].

In the case of the Covid-19 virus, it is hypothesised that AgNPs will bind the spike glycoprotein virus so inhibited virus binding to cells and the release of Nanosilver can decrease the pH of the respiratory epithelial environment (where the COVID-19 virus normally resides) to become more acidic, which is hostile to the virus [27].

Increase immunity

Besides antimicrobial and antiviral effects, Nanosilver is also known as an immune system booster. Nanosilver can modulate the immune system of human cells by regulating inflammation, which can help the inhibition of microorganisms [28]. The proof of AgNPs having an immunomodulatory effect have been reported (Edwards-Jones 2009). Silver ions can increase the ability of immune cells to digest infection agents. Besides that, silver also plays an essential role in stimulating the lymphatic system. It is an essential part of the immune system because it can filters out the toxins from the circulatory system in the body [29].

Combining the two components of gold and silver nanoparticles will have a very beneficial effect. The presence of antigen activity, antibacterial and antiviral effect can build and increase body immunity. The effect of both Nanogold and Nanosilver nanoparticles on coronavirus activity can inhibit the binding of viruses to host cell surface receptors. In this case, ACE2 is a receptor that has a vital role in the entry of Coronavirus into host cells. So, this inhibition can reduce ACE2 levels to help against infection and develop antibodies to fight ACE2 [30].

4. CONCLUSION

It concluded that consuming nanogold-nanosilver health water successfully reduced the average high blood pressure of the volunteers. It also decreases symptoms of hypertension such as dizziness, headache, vertigo, etc. The decrease in the average high blood pressure of the community and the disappearance of symptoms indicate an improvement in the volunteers' health by increasing the body's immunity. With increasing immunity, the body will be stronger against viral infections like Coronavirus.

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