



## The Effect of *Nanogold-Nanosilver* Injection on Increasing the Immunity of Community Affected by Covid-19

Filza Qurrota 'Aini<sup>1</sup>, Titik Taufikurohmah<sup>2</sup>

<sup>1,2</sup> Department of Chemistry, Faculty Mathematics and Natural Sciences, Universitas Negeri Surabaya, Indonesia

**ABSTRACT:** This study aims to determine the best concentration of *Nanogold* and the effect of *Nanogold-Nanosilver* injection on increasing the immune system of people affected by Covid-19. The method used is quantitative and quantitative descriptive by observing the progress of giving injections once a month (May – November 2021) regarding the complaints experienced. The best concentration of *Nanogold* for injection observed on the antioxidant activity and  $\lambda$  maximum stability of *Nanogold* solution 5, 10, 15, 20, 25, 30 ppm after synthesis and after being stored for 7 days using UV-Vis Spectrophotometry instruments. Produce antioxidant activity 44,21%; 47,88%; 51,37%; 52,32%; 56,16%; 61,57%, with an IC<sub>50</sub> of 14 ppm and a  $\lambda$  maximum stability of 5 - 20 ppm is stable; 25 - 30 ppm shifted by 0,50 nm. So, the best concentration of *Nanogold* was 20 ppm which was then characterized using the TEM instrument, resulting in an average size of 22,67 nm. A mixture of *Nanogold-Nanosilver* was injected into the respondents and obtained interview data after each injection. Respondents acknowledged that there was a significant difference, as evidenced by the percentage of development of body condition getting better. Thus, *Nanogold* and *Nanosilver* materials can increase immunity during the Covid-19 pandemic.

**KEYWORDS:** Covid-19, Immune, Injection, *Nanogold*, *Nanosilver*

### INTRODUCTION

Covid-19 is the worst pandemic disease in millennials [1], so it was designated as a global health emergency or PHEIC on March 11, 2020 [2,3]. Coronavirus is a positive-sense RNA virus whose surface is covered with spike-like protrusions ranging from 60 nm to 140 nm in diameter so that it looks like a crown [4].

So that, in the current era, it is needed to use vaccines. Besides that also need drugs, vitamins, supplements, and additional food to strengthen health, especially immunity [14]. Among them, are *Nanogold* and *Nanosilver*-based nanoparticles which have been widely used in various medical application [7]. Because, nanoparticles are the current material that is often considered by researchers [5], which are particles with a size between 1-100 nm [6]. To improve the physical, mechanical, and chemical properties without damaging the atomic structure. And will be more reactive because it has a greater opportunity to interact with other materials [5]. Nanoparticles that play a role in increasing immunity include gold nanoparticles (*Nanogold*) and silver nanoparticles (*Nanosilver*) which have been widely used in various medical applications [6].

*Nanogold* plays a role in drug delivery systems. Its antioxidant activity is 10 times greater than that of vitamin E and has been used in pharmaceutical products including drugs [8]. *Nanogold* works to increase the immune system at the cellular level [9]. Its toxicity tests in vitro and in vivo explain that *Nanogold* is safe to use in the body [10]. While *Nanosilver* has been widely used in agriculture and medicine which have antibacterial, antifungal, antiviral, anti-inflammatory, antiangiogenic, and anti-cancer properties [11,12]. Morphological properties of a nanoparticle can be known in terms of shape and size which were analyzed using FE-SEM and TEM (Transmission Electron Microscopy) microscopic techniques [13].

There are many procedures for administering drugs or vitamins into the body, one of which is often used, namely through intramuscular injection [15]. These procedures are usually used for therapy, vaccines, immune suppression, vitamins, antibiotics, and so on. The procedure is carried out by inserting a needle through the skin surface until it enters the muscle layer to increase the drug absorption and bioavailability compared to oral and other procedures [16].

The combination of the two nanoparticles can inhibit viruses from reaching host cell surface receptors because they can help fight infection and develop antibodies in the body [5]. Thus, this study aims to determine the best concentration of *Nanogold* to be used and to determine the effect of administering *Nanogold-Nanosilver* injections on increasing the immunity of people affected by Covid-19.



## **MATERIALS AND METHODS**

### **Materials and Instrumentations**

The materials used in this study include HAuCl<sub>4</sub>, Sodium Citrate, AgNO<sub>3</sub>, DPPH, ethanol (96%), and aquades. Meanwhile, the equipment used in this study included a 100 mL beaker glass, watch glass, 50 mL measuring cup, dropper, funnel, micropipette, blue tip, 50 mL volumetric flask, test tube, oven, hot plate, spatula, analytical balance, injection, UV-Vis Spectrophotometer and TEM (Jeol type JEM 1400).

### **Methods**

#### ***Synthesis of Gold Nanoparticles (Nanogold)***

*Nanogold* was synthesized from the basic material of HAuCl<sub>4</sub> 1000 ppm which is yellow. Then heated 100 mL of distilled water in a beaker glass until boiling, then added 0.5 mL, 1 mL, 1.5 mL, 2 mL, 2.5 mL, and 3 mL of 1000 ppm HAuCl<sub>4</sub> in each beaker containing boiling distilled water. so that it becomes a *Nanogold* solution with concentrations of 5, 10, 15, 20, 25, and 30 ppm. After that, 2 grams of sodium citrate were added to each solution. Stir and leave until the color changes from yellow to burgundy (red *Nanogold*) [17].

#### ***Synthesis of Silver Nanoparticles (Nanosilver)***

*Nanosilver* was synthesized from colorless 1000 ppm AgNO<sub>3</sub> as the base material. Heated 100 mL of distilled water in a beaker until it boiled, then added 2 mL of 1000 ppm AgNO<sub>3</sub> so that it became a *Nanosilver* solution with a concentration of 20 ppm. After that added 2 grams of sodium citrate. Stir and leave until the solution color changes to yellow [18].

#### ***Nanogold Antioxidant Activity Test***

0.002 grams of DPPH crystals were dissolved in a 50 ml volumetric flask using ethanol to obtain a 0.004% DPPH solution. 2 ml of *Nanogold* sample was added with 1 ml of 0.004% DPPH solution and the incubation process was carried out for 30 minutes at room temperature. Then read the absorbance using UV-Vis spectrophotometry at the maximum wavelength of the DPPH solution (517 nm) [19].

#### ***Nanogold characterization using UV-Vis Spectrophotometry and TEM***

The characterization of the stability of the *Nanogold* solution was observed through the difference in maximum (wavelength) between the initial synthesis and after being stored for 7 days using UV-Vis Spectrophotometry. While the characterization of the shape and size of 20 ppm *Nanogold* was observed using a TEM instrument with a magnification scale of up to 20 nm [20].

#### ***Immune Test***

The type of solution injected in this immune test is a mixture of 20 ppm *Nanogold* and 20 ppm *Nanosilver* with a 9:1 ratio of 3 cc per injection [21]. This test is carried out in the Gununganyar area of Surabaya once a month for 7 months, starting from May - November 2021. The injection is given to people of all ages who are willing to be respondents. The indicator is the improvement of public health conditions for the better [22].

## **RESULT AND DISCUSSION**

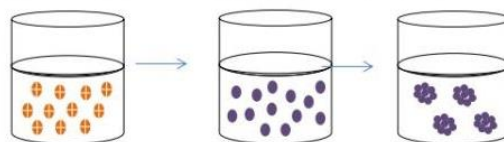
### ***Synthesis of Gold Nanoparticles (Nanogold)***

*Nanogold* is one type of nanoparticle that is easily synthesized [7]. There are many methods in the synthesis of nanoparticles, which generally use physical, chemical, and biological methods [12]. This synthesis uses a chemical method which is the most popular method that is still used today. The method was discovered by Turkevich in 1951 [23].

This method involves three main components, namely 1000 ppm HAuCl<sub>4</sub> as a metal precursor (basic material) and sodium citrate as a reducing agent as well as a stabilizer so that the *Nanogold* solution is not easily aggregated [24]. Sodium citrate acts as a reducing agent by reducing the gold metal ion (Au<sup>3+</sup>) HAuCl<sub>4</sub> to an uncharged gold atom (Au<sup>0</sup>). Au<sup>0</sup> will combine to form clusters that continue to experience nano-sized cluster enlargement [25]. The strength of the reducing agent plays an important role in controlling the reaction rate, thereby influencing the morphology obtained [23].

In addition, it also acts as a stabilizer so that *Nanogold* is not easily aggregated because negative mutants of citrate ions will surround the *Nanogold* surface [19]. The reaction that occurs is  $2\text{Au}^{3+} + 4\text{C}_6\text{H}_5\text{O}_7^{3-} + 6\text{H}_2\text{O} \rightarrow 2\text{Au} + 4\text{C}_6\text{H}_5\text{O}_7 + 3\text{O}_2$  [25].

When gold ions (Au<sup>3+</sup>) are reduced by sodium citrate to form neutral gold atoms (Au<sup>0</sup>), the atoms will be closer to each other through intermolecular bonds. The longer the cluster will grow and form a nanometer size [24].



**Figure 1.** Illustration of *Nanogold* cluster formation

The higher the concentration of *Nanogold*, the smaller the distance between the clusters and the more *Nanogold* clusters formed. So that the resulting color will be more concentrated or stronger [24].



**Figure 2.** Synthesis of *Nanogold* 5, 10, 15, 20, 25, 30 ppm

The *Nanogold* synthesis process changes its color to burgundy as shown in Figure 2. This is following the theory that *Nanogold* has a characteristic burgundy color [6]. To determine the best concentration of *Nanogold*, it can be seen based on the differences that occur after being stored for 7 days.



**Figure 3.** *Nanogold* solution after 7 days storage

Based on Figure 3, it can be seen that the *Nanogold* solution with concentrations of 5, 10, 15, and 20 ppm faded slightly. Meanwhile, at concentrations of 25 and 30 ppm, the color remained burgundy, even darker and there was little precipitate.

This is appropriate, where the *Nanogold* solution with a concentration above 20 ppm if left for several hours or even a few days will form a precipitate, which means the *Nanogold* solution is not homogeneous and undergoes aggregation to form a non-nano particle [26].

#### **Synthesis of Silver Nanoparticles (Nanosilver)**

The *Nanosilver* synthesis process also uses the same method as the *Nanogold* synthesis, namely the chemical method. Where there are three main components, namely,  $\text{AgNO}_3$  1000 ppm as a metal precursor (basic material), sodium citrate as a reducing agent as well as a stabilizer. Sodium citrate will reduce silver metal ions ( $\text{Ag}^+$ ) to uncharged silver atoms ( $\text{Ag}^0$ ). In addition, citrate ions will also react with silver ions to form a complex  $[(\text{Ag})_2] + \dots (\text{citrate}^+)$  so that it will coat and protect the formed *Nanosilver* so that agglomeration does not occur. The reaction that occurs is  $4\text{Ag} + \text{C}_6\text{H}_5\text{O}_7\text{Na}_3 + 2\text{H}_2\text{O} \rightarrow 4\text{Ag}^0 + \text{C}_6\text{H}_5\text{O}_7\text{H}_3 + 3\text{Na}^+ + \text{H}^+ + \text{O}_2\uparrow$  [18]. Reducing agents and stabilizing agents can affect the size and stability of nanoparticles [27].



**Figure 4.** Synthesis of *Nanosilver* 20 ppm

The *Nanosilver* synthesis process occurs when the color changes from a colorless  $\text{AgNO}_3$  base solution to a yellow color. The advantages of synthesizing nanoparticles using chemical methods are easy and inexpensive [12].

#### *Nanogold* Antioxidant Activity Test

The antioxidant activity of *Nanogold* was tested using the DPPH test method. The instrument used in this method is a UV-Vis Spectrophotometer. The DPPH concentration used was 0.004% with a maximum wavelength of 517.00 nm and an absorbance of 0.7041 as shown in Figure 5.

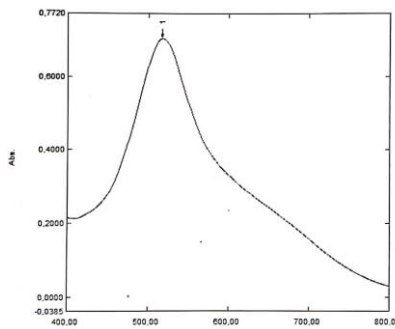
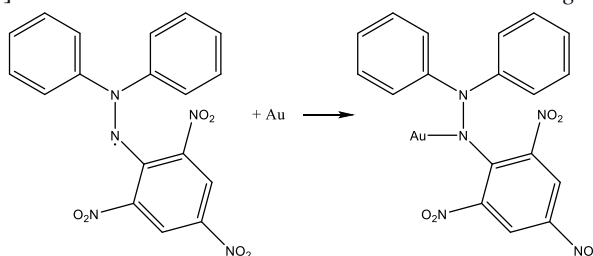


Figure 5. The maximum wavelength spectrum of DPPH

The maximum wavelength is used to read the absorbance of the sample which reduces free radicals. While the absorbance value obtained, will be used as absorbance blank in the calculation of % inhibition.

The antioxidant activity of *Nanogold* was tested by mixing 2 mL of *Nanogold* samples with concentrations of 5, 10, 15, 20, 25, 30 ppm with 1 mL of 0.004% DPPH solution. The mixture was shaken until homogeneous and incubated for 30 minutes at room temperature so that the DPPH could react with the *Nanogold* sample. Then the absorbance was read using a UV-Vis spectrophotometer at the maximum wavelength of DPPH, which is 517 nm.

*Nanogold* is a synthetic antioxidant compound that does not have a carcinogenic effect and has strong, long-lasting activity, and is a very effective antioxidant to reduce free radicals. The higher the concentration of *Nanogold*, the percentage of attenuation against free radicals will increase [25]. The reactions that occur between DPPH and *Nanogold* solution are:

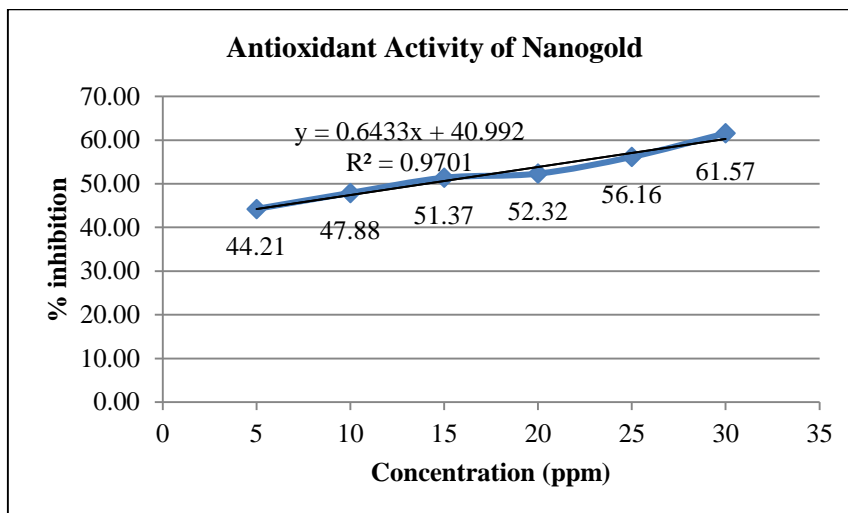


The ability of a compound to scavenge or scavenge DPPH free radicals can be expressed as a percentage of inhibition or a percentage of reduction [28].

$$\% \text{ inhibition} = \frac{Abs_{kontrol} - Abs_{sampel}}{Abs_{kontrol}} \times 100\%$$

Table 1. *Nanogold* antioxidant test results

Concentration (ppm)	Abs		% Inhibition
	Control	Sample	
5	0,8659	0,4831	44.21
10		0,4513	47.88
15		0,4211	51.37
20		0,4129	52.32
25		0,3796	56.16
30		0,3328	61.57



From the curve, a straight line equation is obtained which is then used to calculate the IC<sub>50</sub> value, by calculating the x value where the y value = 50. The IC<sub>50</sub> value is the concentration of a compound needed to inhibit 50% of DPPH free radicals [29]. The IC<sub>50</sub> value produced from *Nanogold* is 14.0028 ppm. So, it can be seen that nanogold is a very strong antioxidant. Where <50 is very strong, 50-100 is strong, 100-150 is currently, 150-200 is weak, and >200 is very weak [38]. The antioxidant activity of *Nanogold* produced is 4 times better than the antioxidant activity of Vitamin E, which is 57.45 ppm [30].

#### *Nanogold* characterization using UV-Vis Spectrophotometry and TEM

The characterization of *Nanogold* can be observed using a UV-Vis Spectrophotometer instrument. This characterization aims to determine the stability of the observed *Nanogold* solution through the maximum (wavelength).

There is a slight difference in the  $\lambda$  maximum of the nanogold solution between the initial synthesis and after being stored for 7 days, as shown in Table 2.

**Table 2.**  $\lambda$  (wavelength) maximum *Nanogold* solution

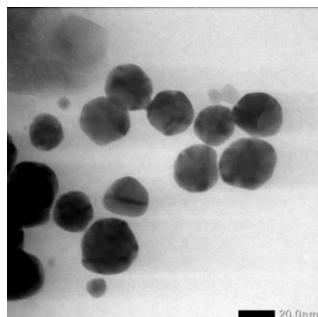
Concentration (ppm)	$\lambda$ maximum (nm)		
	Initial results	synthesis	Synthesis results after 7 days of storage
5	528,50		528,50
10	529,50		529,50
15	530,00		530,00
20	530,50		530,50
25	524,50		525,00
30	524,50		525,00

*Nanogold* solutions with concentrations of 5, 10, 15, and 20 ppm had a maximum that was stable and did not shift. Meanwhile, the maximum at concentrations of 25 and 30 ppm shifted by 0.50 nm.

The *Nanogold* characterization process can also be observed through the shape and size of TEM analysis. TEM can see the size of a particle to nano size with a magnification of up to 150,000,000 times [20].

Based on the stability and antioxidant activity produced, it is known that the best concentration of *Nanogold* solution is 20 ppm. Where at a concentration of 20 ppm, it has a stability that is seen based on the maximum that does not shift and the percentage of inhibition is 52.32%. Thus, to determine the size of the nanoparticles, it is enough to look at a concentration of 20 ppm.





**Figure 6.** TEM photo results of 20 ppm *Nanogold* solution with a magnification scale of 20.0 nm

Based on Figure 6, it can be seen that there are 14 nanogold clusters of various sizes shaped like a circle, with an average size of 22.6701 nm. The results obtained are following the theory, where the nanoparticle size ranges from 1-100 nm and the nanogold size is around 20.68 nm [17].

#### Immune Test

The type of solution injected in this immune test is a mixture of 20 ppm *Nanogold* and 20 ppm *Nanosilver* with a 9:1 ratio of 3 cc per injection [21]. Only 1 part of the *Nanosilver* is used, because *Nanosilver* acts as a stabilizer and preservative which has stable properties and has potential applications in various fields, including as a catalyst and antibacterial agent [31].

This procedure is carried out with observations regarding immunity body of respondents conducted in the Gununganyar area of Surabaya once a month for 7 months, starting from May – November 2021, following relevant laws and institutional guidelines, and respondents have obtained informed consent.



**Figure 7.** *Nanogold-Nanosilver* Injection Activities

Based on interview data, there were several complaints experienced by respondents before being given a *Nanogold-Nanosilver* injection.

**Table 3.** List of respondent's complaints

Complain	Frequency (person)	Percentage (%)
Exposed to Covid-19	1	1,8
Tremor	1	1,8
Vertigo	1	1,8
Maag	5	6
Tonsils	2	2,4



Dizzy	3	3,6
Cough	4	4,8
Sneeze	1	1,8
Menstruation (painful and irregular)	2	2,4
Face (acne, spots, and dullness)	24	28,9
Body fitness	39	46,9
<b>Total</b>	<b>83</b>	<b>100</b>

The largest percentage of complaints experienced by respondents is about body fitness or commonly said to have low body resistance as many as 39 people (46.9%). Where, respondents feel more easily sleepy, tired, weak, and not feeling well. Meanwhile, the smallest percentage was exposed to Covid-19, tremor, vertigo, and sneezing as many as 1 person each (1.8%).

After being given the injection 7 times, observations were made again by interviewing respondents about the development of complaints experienced as written in table 4.

**Table 4.** Percentage of progress of respondents complaints

Complain	May	June	July	August	September	October	November
Exposed to Covid-19	5%	10%	20%	30%	45%	60%	75%
Tremor	5%	10%	20%	30%	45%	60%	75%
Vertigo	5%	10%	20%	30%	45%	60%	75%
Maag	10%	20%	30%	45%	60%	75%	95%
Tonsils	10%	25%	40%	55%	70%	85%	99%
Dizzy	15%	25%	35%	50%	65%	85%	99%
Cough	15%	25%	40%	55%	70%	85%	99%
Sneeze	10%	20%	30%	45%	60%	75%	95%
Menstruation (painful and irregular)	10%	20%	35%	50%	65%	80%	99%
Face (acne, spots, and dullness)	15%	30%	45%	60%	75%	90%	99%
Body fitness	20%	30%	40%	55%	70%	85%	99%

Description:

Indicator 0-24%: progress is very little improved (still relapses often)

Indicator 25-49%: progress slightly improved (reduced complaints and do not recur frequently)

Indicator 50-74%: progress is improving (rarely relapse or pain)

Indicator 75-99%: very good progress (complaints disappear)

Based on the data in table 4, proves that injection of *Nanogold Nanosilver* is a material that can increase immunity in people affected by Covid-19, where body conditions are getting better. This is because *Nanogold* materials work to increase the immune system at the cellular level by building complexes with glutathione in cells [9]. Glutathione is a natural antioxidant that is in cells and plays a role in the process, formation, division, proliferation, and defense of T lymphocyte cells to fight pathogens [22].



*Nanogold* can conjugate with glutathione, which is an endogenous antioxidant in cells to reduce free radicals and reduce cell damage. Also plays a role in stabilizing ATP which is a source of cell energy so that it can activate metabolic processes in a healthy state [8]. An increase in the immune system and the presence of T cells in the body will detect, search for, and destroy incoming pathogens. So that someone who previously had a complaint (disease) will recover. Whereas someone who was previously healthy, his body will be better at fighting pathogens that will enter the body [22].

In addition to *Nanogold* material, there is also a *Nanosilver* material that acts as a catalyst in the immune system as an antiviral that can help reduce symptoms and infectivity and reduce the duration of the disease. The way it works is by stopping the viral replication cycle at various stages [32]. The antiviral properties of *Nanosilver* make it able to bind to the surface of viral proteins and break disulfide bonds so that it disrupts protein stability and affects virus infectivity or in other words, works to disrupt the virus replica system so that the activity of multiplying viruses. will be stopped by releasing silver ions which can inhibit enzymatic activity and then destroy the protein structure of the viral cell. So that with increased immunity, the remaining viruses will be easier to fight and can inhibit or eliminate the virus [33,9]

So, there are two ways *Nanosilver* interacts with viral pathogens, namely:

- 1) Silver nanoparticles will bind to the outer layer of the virus thereby inhibiting the attachment of the virus to cell receptors, and
- 2) Silver nanoparticles will bind to viral DNA or RNA so that it inhibits the replication or spread of the virus in the host cell [34]

The *Nanogold-Nanosilver* injection procedure is carried out by inserting a syringe through the skin surface until it enters the muscle layer which causes the drug to be absorbed quickly because the muscle has many blood vessels [21,35]. Drugs that are injected into the muscle will form drug deposits which are then absorbed gradually into the blood vessels [36].

Because the virus is one of the things that can interfere with the immune system that comes from outside the body [37], the combination of the two materials is very good because it can strengthen the immune system. Where, the body will not be easily affected by disease or exposure to viruses, especially during the Covid-19 pandemic.

## CONCLUSION

Synthesis of *Nanogold* with concentrations of 5, 10, 15, 20, 25, and 30 ppm produce antioxidant activity 44,21%; 47,88%; 51,37%; 52,32%; 56,16%; 61,57%, with an IC<sub>50</sub> of 14 ppm, and a  $\lambda$  maximum stability of 5, 10, 15, 20 ppm after synthesis and after being stored for 7 days is stable; 25, 30 ppm shifted by 0,50 nm. So, the best concentration of *Nanogold* was 20 ppm which was then characterized using the TEM instrument, resulting in an average size of 22,67 nm. In addition, the administration of *Nanogold-Nanosilver* injections to communities affected by Covid-19 in Gununganyar, Surabaya has a very significant effect on increasing immunity as evidenced by the percentage of development of body condition getting better. Thus, *Nanogold* and *Nanosilver* materials can increase immunity during the Covid-19 pandemic and in the future can be used as future drugs.

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