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Regards,



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Submitted to the journal "Eureka Herba Indonesia (July 20<sup>th</sup>, 2022)

**Meniran Potential (*Phyllanthus niruri* L.) and Sambiloto (*Andrographis paniculata*) as a Supplement to The Management of Coronavirus Disease 2019 (COVID 19)**

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**Abstract**

COVID-19 infection, both moderate and severe symptoms, can cause pneumonia with an opaque picture that can be detected in thoracic CT scans, pulmonary edema and accumulation of pleural fluid in the lungs. The use of herbs as health drinks is thought to play a role in increasing the body's immunity. The meniran plant (*Phyllanthus niruri*) contains tannins and flavonoids that are efficacious as immunomodulators. Meanwhile, sambiloto also contains chemical compounds alkaloids, carbohydrates, resins, saponins, flavonoids, steroids, glycosides and tannins. Meniran and sambiloto herbs have the potential to increase the immune system, potentially being developed as a supplement to covid-19 management.

**Keywords:** *Andrographis paniculata*, COVID-19, Immunomodulator, *Phyllanthus niruri*.

**1.Introduction**

In December 2019 there was a report of coronavirus from the city of Wuhan, Hubei province, China. This virus has become a pandemic that has spread throughout the world until now. The name COVID 19 stands for corona virus diseases 2019 or also known as SARS-Cov-2. While this research is being carried out, COVID-19 cases are increasing to reach 96.2 million in the world, 977 thousand positive cases in Indonesia and 13,599 thousand positive cases in South Sumatra. COVID 19 infection, both moderate and severe symptoms, can cause pneumonia with an opaque picture that can be detected in thoracic CT scans, pulmonary edema and accumulation of pleural fluid in the lungs. The genetic sequence of SARS-CoV-2, shows that COVID 19 belongs to the genus  $\beta$ -coronavirus, with 79% of nucleotide identities being SARS-CoV and 51.8% identity to MERS-CoV. Inoculation with SARS-CoV-2 from human respiratory tract epithelial cells in

in vitro causes a stopathic effect and a halt in ciliary movement of respiratory epithelial cells, similar to the cytopathic effect observed in SARS-CoV infection.<sup>1</sup>

Indonesia is one of the countries with a large diversity of biological wealth. No less than 30,000 species of plants exist in the tropical forests of Indonesia. Of these, around 9,600 species are known to have medicinal properties but not all of them are optimally utilized as herbal medicine. The use of herbs is as a medicine in the form of steeping herbs, herbs, standardized herbal medicines and phytopharmaceuticals. Jamu is the cultural heritage of the Indonesian nation, which traditionally and for generations has been used to improve the degree of health.<sup>2,3</sup> Various plants with health potential have been studied related to utilization in improving the degree of body health, including triggering the body's immunity in the face of COVID 19.

## **2. Benefits of Meniran (*Phyllanthus niruri* L.)**

*Phyllanthus niruri* L. is often referred to as *meniran*, *supported by children*, *leaves of child carriers*, *gosau ma dung-dung*. The plant has a chemical content of tannins, resin, potassium, flavonoids (quercetin, quersitrin, isocuersitrin, astragalin, rutin; *kaemferol-4-ramnopiranosid*, *erythrol-7-ramnopiranosid*), and lignans (kubebin dimethyl ether, urinatetralin, nirurin, nirurid, filantin, pituitary, triterpene lup-20-en-3-b-o). The leaves, roots and all parts of this plant can be used empirically for the treatment of ayan, malaria, constipation, high blood pressure, irregular menstruation, thrush (the leaves), heartburn, tooth pain (the root), less smooth urine, gonorrhea, rajasinga, kidney pain, splinting, fever, tetanus, dirty blood, gagau seizures, egg whites in the urine, stone urine (all its parts) and others.<sup>4</sup>

In testing the immunostimulant effect of meniran water extract *in vivo* using mujair fish (*Oreochromis mossambicus*) at a dose range of 0.002 – 20 mg showed a significant increase in neutrophil activation and antibody response. Based on the observations, fish with a test dose of 20 mg / kg BB showed a maximum increase in the primary and secondary response of antibodies and a dose of 0.002 mg / kg showed higher neutrophil activation than the control group. The results of this test indicate that meniran extract has potential as an immunostimulant.<sup>5th</sup>

In vitro research using PBMC (peripheral blood mononuclear cells) and macrophage cells of TB patients showed that the aqueous extract of *Phyllanthus niruri* L. leaves had immunomodulatory activity with an increase in PBMC cell proliferation, increased phagocytic activity, and the addition of no macrophage release (dose-dependent effect). Clinical trials have

also been carried out in a number of hospitals in Jakarta and Surabaya, it is reported that adjuvant therapy or companion therapy is a drug that is consumed to support the effect of the main drug because it is known to increase the potential of the main drug. Meniran extract successfully shortens the treatment period in several diseases such as tuberculosis, hepatitis and candidiasis vaginalis. The addition of meniran extract to antituberculosis drugs for post-hemorrhoidal pulmonary TB patients can encourage changes in acid-resistant bacillus (BTA) three times greater. The results of clinical testing showed that patients who received anti-tuberculosis drugs along with 50 mg of meniran extract, recovered at week 6 while patients who only received anti-tuberculosis drugs recovered at week 14. Furthermore, it was reported that there was no difference in side effects significantly with the two treatments, in other words, the administration of meniran extract combined with standard antituberculosis drugs was quite safe. <sup>6th</sup>

Based on testing of antiviral activity in mice, it is known that the administration of *Phyllanthus niruri* L. water extract intraperitoneal is effective in inhibiting woodchuck viral hepatitis (WHV) where 3 out of 4 test animals experienced a decrease and elimination of surface activity of titer antigen surfaces and DNA polymerase in serum for 3-6 weeks, and no more WHV was detected at week 45 after previous administration was stopped at week 10.

Based on tests conducted on mice, it is known that the administration of hexane extract, kayalignan fraction or lignin phytertralin meniran orally provides a consistent antioxidant effect in fighting inflammatory causative agents in the legs of mice characterized by inhibition to an increase in IL-1 $\beta$ .

Based on the results of in vivo testing of mice (nimesulide-induced oxidative stress), the results were obtained that the administration of aqueous extract has antioxidant activity and protects the liver from damage due to nimesulide through the regulation of oxidative stress in the liver. Intraperitoneal administration showed more effective results than oral administration of the preparation. Other tests in vivo showed the antioxidant activity of meniran water extract against liver mice damage induced by paracetamol, the mechanism is through the reduction of glutamate oxaloacetate transaminase (GOT) and glutamate pyruvate transaminase (GPT) serum, and increased catalase activity in the liver of the test group.

Usen meniran sa dekokta, 15-30 g of herbaceous meniran in 250 mL of water, taken 2-3 times per day. Dekokta is a liquid preparation made by extracting herbal preparations with water at a temperature of 90°C for 30 minutes. Side effects of meniran in the form of hipoglikemi,

hypotension, electrolyte and mineral imbalances. Meniran can interact in the form of an increase in the effects of insulin and diabetes medications if used together. Meniran contains geraniin which are reported to have negative inotropic, negative chronotropic, hypotensive effects and ACE inhibitors, therefore, it is likely to enhance the effects of antihypertensive drugs,  $\alpha$ -blockers and heart drugs. Meniran herbaceous ethanol extract can inhibit cytochrome P450 enzymes *in vivo* and *in vitro*. Meniran has a synergistic effect with antimicrobial drugs, antagonists with corticosteroids (immunosuppressant agents).

### 3. Benefits of Sambiloto (*Andrographis paniculata*)

Sambiloto belongs to the genus *Andrographis* and the tribe *Acanthaceae*. The scientific name of the medicinal plant sambiloto is *Andrographis paniculata*. The popularity of the sambiloto plant in Indonesia causes several regions / ethnicities in Indonesia to have different mentions of names, for example, as in Java it is known as Ki oray, ki peurat, takilo (Sundanese), bidara, sadilata, sambilata, takila (Javanese). While the name sambiloto in English is *green chireta*, *king of bitters*, while in Thailand it is called *fa thalaai*, in the Philippines it is called *aluy* and in France it is known by the name *roi des amers*. The chemical content of sambiloto simplicia includes lactone terpenoids which include andrographolide, deoxy cyandrographolida, 11, 12-didehydro-14-deoxysiandrographolide, neoandrografolide, andrographicide, deoxy cyandrographicide and androropanocide. With andrographolide identity compounds. Sambiloto also contains chemical compounds alkaloids, carbohydrates, resins, saponins, flavonoids, steroids, glycosides and tannins. The use of herbs described in pharmacopoeias and certain official documents namely: for bacillary dysentery, bronchitis, ulcers, enteritis, cough, dyspepsia, fever, hepatitis, malaria, wounds on the mouth, wounds, tuberculosis and snake venomous bites; in folk medicine it is used for colic, otitis media, vaginitis, pelvic inflammatory diseases, chickenpox, eczema and burns. The plant is used for tonsil inflammation, ulcers, typhoid, fever, hives, bitten by insects or vipers, diabetes, dysentery, ear inflammation, appendicitis, colds, dirty blood. <sup>7th</sup>

Herbaceous sambiloto (*Andrographis paniculata* Burm. Nees) contains many components of chemical compounds that have been widely researched with activity as a hepatoprotector and one of its active substances, namely *andrographolids*. Research that aims to determine the activity of *A. paniculata* that have activity as immunomodulators and hepatoprotectors against balb/c mice that have been induced hepatitis B vaccines show that n-hexane extract (2.7 mg / 20 g BB

mice) showed the highest increase in IgG. The three most active fractions of n-hexane showed the highest to lowest increase in the amount of IgG, namely: F2 (containing terpenoid compounds, steroids and flavonoids) IgG levels of 0.569 mg / 20 g BB mice, F1 (containing terpenoid compounds) IgG levels of 0.126 mg / 20 g BB mice, F4 (containing alkaloid and terpenoid compounds) IgG levels of 0.094 mg / 20 g BB mice. Studies have been conducted on the immunomodulatory effect of andrographolida compounds on innate and adaptive immune responses using mice at a dose of 1 mg / kg. From the study, the results were obtained that there was a decrease in the production of anti-HBs antibodies and the number of IL-4-producing splenocytes. Andrographolidas can modulate innate and adaptive immune responses by regulating the phenotypic polarization of macrophages and the production of Ag-specific antibodies. <sup>8,9</sup>

A double-disguised, randomized controlled clinical trial of *A. paniculata* extract has been conducted in patients with uncomplicated upper respiratory tract infections, with a total of 223 patients involved divided into two groups (placebo, and *A. paniculata* extract group (200 mg/day)). From clinical studies it was shown that *A. paniculata extract* is effective for reducing symptoms of upper respiratory tract infections with an effectiveness of 2.1 times (52.7 %) higher than placebo. A clinical trial of andrographolide was conducted to examine 13 HIV-positive patients and five healthy volunteers who were HIV-negative. The study began with a dose of 5 mg/kgbb for the first 3 weeks, then increased to 10 mg/kgbb for 3 weeks, and then increased to 20 mg/kgbb for the last 3 weeks. Administration of andrographolida significantly increased the number of CD4 + lymphocytes from an initial average of 405 to 501 in HIV-positive patients. There were no statistically significant changes in the average rate of HIV-1 viral load in the blood. A recent study summarized that andrographolide derivatives may be promising candidates for preventing HIV infection, suggesting that andrographolids inhibit the fusion of HL2/3 cells mediated by gp120 with T2M-bl cells. <sup>10,11</sup>

Several studies have reported the antioxidant activity of *A. paniculata* and its constituents. <sup>9,10</sup> *A. paniculata* aqueous extract significantly increases the activity of antioxidant defense enzymes such as catalase, superoxide dismutase, and *glutathione-transferase* and reduces glutathione content. This extract significantly inhibits lipid peroxidation by lowering the levels of reactive substances of thibarbituric acid in the liver and kidneys of diabetic rats (compared to normal mice) and also significantly increasing the level of hepatic glutathione concentrations. *Pre-treatment* of andrographolida was reported to significantly attenuate the accumulation of phorbol-

12-myristate-13-acetate- (PMA-) induced formation of ROS and N-formyl-methionyl-leucyl-phenylalanine- (fMLP-) which induced adhesion of rat neutrophils. It was shown in *in vivo* studies, that the administration of andrographolid sulfonates (using water-soluble andrographolidas), intraperitoneally reduced the severity of colitis in rats induced 2-4 trinitrobenzene (TNBS).<sup>12,13 pm</sup>

Usage: 3-9 g of dried herbs or 25-75 g of fresh herbs as a single dose as needed. A total of three grams of dry matter or 25 grams of fresh ingredients are boiled and taken 2 times a day before meals. The unincorporated effect n of the use of high doses of sambiloto herbs can cause stomach discomfort, vomiting, nausea and loss of appetite, this is due to the bitter taste of andrografolida, while in women it can cause an antifertility effect. It has been reported (very rarely) the onset of itching (kaligata/urticaria) and swelling of the eyes after drinking sambiloto decoction. It is recommended to avoid this plant during pregnancy due to the preventive effect of ovulation. Individuals allergic to the plant can even cause anaphylactic reactions. Avoid prolonged use in conjunction with immunosuppressant drugs. Sambiloto herbaceous extract is likely to have a synergistic effect with isoniazid. Sambiloto has hypotensive and antiplatelet effects so that it can enhance the effect of antihypertensive and antiplatelet drugs.

#### **4.Conclusion**

Meniran and sambiloto herbs have the potential to increase the immune system , potentially being developed as a supplement to covid-19 management.

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**Submission acknowledgement**

Dear author(s),

Rachmat Hidayat\*, Patricia Wulandari has submitted the manuscript "Potential of Meniran (*Phyllanthus niruri L.*) and Sambiloto (*Andrographis paniculata*) as a Supplement to the Management of Coronavirus Disease 2019 (COVID-19)" to Eureka Herba Indonesia. The paper will be screened by editor and reviewed by peer review.

Cordially,



Prof. Paula Magnano, PhD

Editor



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**Eureka Herba Indonesia**



**Peer Review Results**

Dear author(s),

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Cordially,

A handwritten signature in black ink, appearing to be "P. Magnano".

Prof. Paula Magnano, PhD

Editor



**HM Publisher**

***(\*) Corresponding author***

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**Abstract** →3

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**1.Introduction** →4

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Herbaceous sambiloto (*Andrographis paniculata* Burm. Nees) contains many components of chemical compounds that have been widely researched with activity as a hepatoprotector and one of its active substances, namely *andrographolids*. Research that aims to determine the activity of *A. paniculata* that have activity as immunomodulators and hepatoprotectors against balb/c mice that have been induced hepatitis B vaccines show that n-hexane extract (2.7 mg / 20 g BB mice) showed the highest increase in IgG. The three most active fractions of n-hexane showed the highest to lowest increase in the amount of IgG, namely: F2 (containing terpenoid compounds,



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A double-disguised, randomized controlled clinical trial of *A. paniculata* extract has been conducted in patients with uncomplicated upper respiratory tract infections, with a total of 223 patients involved divided into two groups (placebo, and *A. paniculata* extract group (200 mg/day)). From clinical studies it was shown that *A. paniculata extract* is effective for reducing symptoms of upper respiratory tract infections with an effectiveness of 2.1 times (52.7 %) higher than placebo. A clinical trial of andrographolide was conducted to examine 13 HIV-positive patients and five healthy volunteers who were HIV-negative. The study began with a dose of 5 mg/kgbb for the first 3 weeks, then increased to 10 mg/kgbb for 3 weeks, and then increased to 20 mg/kgbb for the last 3 weeks. Administration of andrographolida significantly increased the number of CD4 + lymphocytes from an initial average of 405 to 501 in HIV-positive patients. There were no statistically significant changes in the average rate of HIV-1 viral load in the blood. A recent study summarized that andrographolide derivatives may be promising candidates for preventing HIV infection, suggesting that andrographolids inhibit the fusion of HL2/3 cells mediated by gp120 with TZM-bl cells. <sup>10,11</sup>

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that the administration of andrographolid sulfonates (using water-soluble andrographolidas), intraperitoneally reduced the severity of colitis in rats induced 2-4 trinitrobenzene (TNBS).<sup>12,13 pm</sup>

Usage: 3-9 g of dried herbs or 25-75 g of fresh herbs as a single dose as needed. A total of three grams of dry matter or 25 grams of fresh ingredients are boiled and taken 2 times a day before meals. The unincorporated effect n of the use of high doses of sambiloto herbs can cause stomach discomfort, vomiting, nausea and loss of appetite, this is due to the bitter taste of andrografolida, while in women it can cause an antifertility effect. It has been reported (very rarely) the onset of itching (kaligata/urticaria) and swelling of the eyes after drinking sambiloto decoction. It is recommended to avoid this plant during pregnancy due to the preventive effect of ovulation. Individuals allergic to the plant can even cause anaphylactic reactions. Avoid prolonged use in conjunction with immunosuppressant drugs. Sambiloto herbaceous extract is likely to have a synergistic effect with isoniazid. Sambiloto has hypotensive and antiplatelet effects so that it can enhance the effect of antihypertensive and antiplatelet drugs.

#### **4. Conclusion** →5

Meniran and sambiloto herbs have the potential to increase the immune system , potentially being developed as a supplement to covid-19 management.

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## Reviewer 2: Revision required

### **Meniran Potential (*Phyllanthus niruri* L.) and Sambiloto (*Andrographis paniculata*) as a Supplement to The Management of Coronavirus Disease 2019 (COVID 19)** →1

Rachmat Hidayat<sup>1\*</sup>, Patricia Wulandari<sup>2</sup>

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<sup>2</sup>Cattleya Mental Health Center, Palembang, Indonesia

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### **Abstract** →3

COVID-19 infection, both moderate and severe symptoms, can cause pneumonia with an opaque picture that can be detected in thoracic CT scans, pulmonary edema and accumulation of pleural fluid in the lungs. The use of herbs as health drinks is thought to play a role in increasing the body's immunity. The meniran plant (*Phyllanthus niruri*) contains tannins and flavonoids that are efficacious as immunomodulators. Meanwhile, sambiloto also contains chemical compounds alkaloids, carbohydrates, resins, saponins, flavonoids, steroids, glycosides and tannins. Meniran and sambiloto herbs have the potential to increase the immune system, potentially being developed as a supplement to covid-19 management.

**Keywords:** *Andrographis paniculata*, COVID-19, Immunomodulator, *Phyllanthus niruri*. →2

### **1.Introduction** →4

In December 2019 there was a report of coronavirus from the city of Wuhan, Hubei province, China. This virus has become a pandemic that has spread throughout the world until now. The name COVID 19 stands for corona virus diseases 2019 or also known as SARS-Cov-2. While this research is being carried out, COVID-19 cases are increasing to reach 96.2 million in the world, 977 thousand positive cases in Indonesia and 13,599 thousand positive cases in South Sumatra. COVID 19 infection, both moderate and severe symptoms, can cause pneumonia with an opaque picture that can be detected in thoracic CT scans, pulmonary edema and accumulation of pleural fluid in the lungs. The genetic sequence of SARS-CoV-2, shows that COVID 19 belongs to the genus  $\beta$ -coronavirus, with 79% of nucleotide identities being SARS-CoV and 51.8% identity to MERS-CoV. Inoculation with SARS-CoV-2 from human respiratory tract epithelial cells in

vitro causes a stopathic effect and a halt in ciliary movement of respiratory epithelial cells, similar to the cytopathic effect observed in SARS-CoV infection.<sup>1</sup>

Indonesia is one of the countries with a large diversity of biological wealth. No less than 30,000 species of plants exist in the tropical forests of Indonesia. Of these, around 9,600 species are known to have medicinal properties but not all of them are optimally utilized as herbal medicine. The use of herbs is as a medicine in the form of steeping herbs, herbs, standardized herbal medicines and phytopharmaceuticals. Jamu is the cultural heritage of the Indonesian nation, which traditionally and for generations has been used to improve the degree of health.<sup>2,3</sup> Various plants with health potential have been studied related to utilization in improving the degree of body health, including triggering the body's immunity in the face of COVID 19.

## 2. Benefits of Meniran (*Phyllanthus niruri* L.)

*Phyllanthus niruri* L. is often referred to as *meniran*, supported by children, leaves of child carriers, *gosau ma dung-dung*. The plant has a chemical content of tannins, resin, potassium, flavonoids (quercetin, quersitrin, isocuersitrin, astragalin, rutin; *kaemferol-4-ramnopiranosid*, *erythrol-7-ramnopiranosid*), and lignans (kubebin dimethyl ether, urinatetralin, nirurin, nirurid, filantin, pituitary, triterpene lup-20-en-3-b-o). The leaves, roots and all parts of this plant can be used empirically for the treatment of ayan, malaria, constipation, high blood pressure, irregular menstruation, thrush (the leaves), heartburn, tooth pain (the root), less smooth urine, gonorrhea, rajasinga, kidney pain, splinting, fever, tetanus, dirty blood, gagau seizures, egg whites in the urine, stone urine (all its parts) and others.<sup>4</sup>

In testing the immunostimulant effect of meniran water extract *in vivo* using mujair fish (*Oreochromis mossambicus*) at a dose range of 0.002 – 20 mg showed a significant increase in neutrophil activation and antibody response. Based on the observations, fish with a test dose of 20 mg / kg BB showed a maximum increase in the primary and secondary response of antibodies and a dose of 0.002 mg / kg showed higher neutrophil activation than the control group. The results of this test indicate that meniran extract has potential as an immunostimulant.<sup>5th</sup>

In vitro research using PBMC (peripheral blood mononuclear cells) and macrophage cells of TB patients showed that the aqueous extract of *Phyllanthus niruri* L. leaves had immunomodulatory activity with an increase in PBMC cell proliferation, increased phagocytic activity, and the addition of no macrophage release (dose-dependent effect). Clinical trials have

also been carried out in a number of hospitals in Jakarta and Surabaya, it is reported that adjuvant therapy or companion therapy is a drug that is consumed to support the effect of the main drug because it is known to increase the potential of the main drug. Meniran extract successfully shortens the treatment period in several diseases such as tuberculosis, hepatitis and candidiasis vaginalis. The addition of meniran extract to antituberculosis drugs for post-hemorrhoidal pulmonary TB patients can encourage changes in acid-resistant bacillus (BTA) three times greater. The results of clinical testing showed that patients who received anti-tuberculosis drugs along with 50 mg of meniran extract, recovered at week 6 while patients who only received anti-tuberculosis drugs recovered at week 14. Furthermore, it was reported that there was no difference in side effects significantly with the two treatments, in other words, the administration of meniran extract combined with standard antituberculosis drugs was quite safe. <sup>6th</sup>

Based on testing of antiviral activity in mice, it is known that the administration of *Phyllanthus niruri* L. water extract intraperitoneal is effective in inhibiting woodchuck viral hepatitis (WHV) where 3 out of 4 test animals experienced a decrease and elimination of surface activity of titer antigen surfaces and DNA polymerase in serum for 3-6 weeks, and no more WHV was detected at week 45 after previous administration was stopped at week 10.

Based on tests conducted on mice, it is known that the administration of hexane extract, kayalignan fraction or lignin phytertralin meniran orally provides a consistent antioxidant effect in fighting inflammatory causative agents in the legs of mice characterized by inhibition to an increase in IL-1 $\beta$ .

Based on the results of in vivo testing of mice (nimesulide-induced oxidative stress), the results were obtained that the administration of aqueous extract has antioxidant activity and protects the liver from damage due to nimesulide through the regulation of oxidative stress in the liver. Intraperitoneal administration showed more effective results than oral administration of the preparation. Other tests in vivo showed the antioxidant activity of meniran water extract against liver mice damage induced by paracetamol, the mechanism is through the reduction of glutamate oxaloacetate transaminase (GOT) and glutamate pyruvate transaminase (GPT) serum, and increased catalase activity in the liver of the test group.

Usen meniran sa dekokta, 15-30 g of herbaceous meniran in 250 mL of water, taken 2-3 times per day. Dekokta is a liquid preparation made by extracting herbal preparations with water at a temperature of 90°C for 30 minutes. Side effects of meniran in the form of hipoglikemi,

hypotension, electrolyte and mineral imbalances. Meniran can interact in the form of an increase in the effects of insulin and diabetes medications if used together. Meniran contains geraniin which are reported to have negative inotropic, negative chronotropic, hypotensive effects and ACE inhibitors, therefore, it is likely to enhance the effects of antihypertensive drugs,  $\alpha$ -blockers and heart drugs. Meniran herbaceous ethanol extract can inhibit cytochrome P450 enzymes *in vivo* and *in vitro*. Meniran has a synergistic effect with antimicrobial drugs, antagonists with corticosteroids (immunosuppressant agents).

### 3. Benefits of Sambiloto (*Andrographis paniculata*)

Sambiloto belongs to the genus *Andrographis* and the tribe *Acanthaceae*. The scientific name of the medicinal plant sambiloto is *Andrographis paniculata*. The popularity of the sambiloto plant in Indonesia causes several regions / ethnicities in Indonesia to have different mentions of names, for example, as in Java it is known as Ki oray, ki peurat, takilo (Sundanese), bidara, sadilata, sambilata, takila (Javanese). While the name sambiloto in English is *green chireta*, *king of bitters*, while in Thailand it is called *fa thalaai*, in the Philippines it is called *aluy* and in France it is known by the name *roi des amers*. The chemical content of sambiloto simplicia includes lactone terpenoids which include andrographolide, deoxy cyandrographolida, 11, 12-didehydro-14-deoxysiandrographolide, neoandrografolide, andrographicide, deoxy cyandrographicide and androropanocide. With andrographolide identity compounds. Sambiloto also contains chemical compounds alkaloids, carbohydrates, resins, saponins, flavonoids, steroids, glycosides and tannins. The use of herbs described in pharmacopoeias and certain official documents namely: for bacillary dysentery, bronchitis, ulcers, enteritis, cough, dyspepsia, fever, hepatitis, malaria, wounds on the mouth, wounds, tuberculosis and snake venomous bites; in folk medicine it is used for colic, otitis media, vaginitis, pelvic inflammatory diseases, chickenpox, eczema and burns. The plant is used for tonsil inflammation, ulcers, typhoid, fever, hives, bitten by insects or vipers, diabetes, dysentery, ear inflammation, appendicitis, colds, dirty blood. <sup>7th</sup>

Herbaceous sambiloto (*Andrographis paniculata* Burm. Nees) contains many components of chemical compounds that have been widely researched with activity as a hepatoprotector and one of its active substances, namely *andrographolids*. Research that aims to determine the activity of *A. paniculata* that have activity as immunomodulators and hepatoprotectors against balb/c mice that have been induced hepatitis B vaccines show that n-hexane extract (2.7 mg / 20 g BB



mice) showed the highest increase in IgG. The three most active fractions of n-hexane showed the highest to lowest increase in the amount of IgG, namely: F2 (containing terpenoid compounds, steroids and flavonoids) IgG levels of 0.569 mg / 20 g BB mice, F1 (containing terpenoid compounds) IgG levels of 0.126 mg / 20 g BB mice, F4 (containing alkaloid and terpenoid compounds) IgG levels of 0.094 mg / 20 g BB mice. Studies have been conducted on the immunomodulatory effect of andrographolida compounds on innate and adaptive immune responses using mice at a dose of 1 mg / kg. From the study, the results were obtained that there was a decrease in the production of anti-HBs antibodies and the number of IL-4-producing splenocytes. Andrographolidas can modulate innate and adaptive immune responses by regulating the phenotypic polarization of macrophages and the production of Ag-specific antibodies. <sup>8,9</sup>

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Usage: 3-9 g of dried herbs or 25-75 g of fresh herbs as a single dose as needed. A total of three grams of dry matter or 25 grams of fresh ingredients are boiled and taken 2 times a day before meals. The unincorporated effect n of the use of high doses of sambiloto herbs can cause stomach discomfort, vomiting, nausea and loss of appetite, this is due to the bitter taste of andrografolida, while in women it can cause an antifertility effect. It has been reported (very rarely) the onset of itching (kaligata/urticaria) and swelling of the eyes after drinking sambiloto decoction. It is recommended to avoid this plant during pregnancy due to the preventive effect of ovulation. Individuals allergic to the plant can even cause anaphylactic reactions. Avoid prolonged use in conjunction with immunosuppressant drugs. Sambiloto herbaceous extract is likely to have a synergistic effect with isoniazid. Sambiloto has hypotensive and antiplatelet effects so that it can enhance the effect of antihypertensive and antiplatelet drugs.

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## Potential of Meniran (*Phyllanthus niruri* L.) and Sambiloto (*Andrographis paniculata*) as a Supplement to the Management of Coronavirus Disease 2019 (COVID-19)

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### ABSTRACT

COVID-19 infection with moderate or severe symptoms can cause pneumonia with an opaque appearance that can be detected on a chest CT scan, pulmonary edema, and accumulation of pleural fluid in the lungs. The use of herbs as health drinks is thought to play a role in increasing the body's immunity. Meniran plant (*Phyllanthus niruri*) contains tannins and flavonoids, which are efficacious as immunomodulators. Meanwhile, sambiloto also contains chemical compounds of alkaloids, carbohydrates, resins, saponins, flavonoids, steroids, glycosides, and tannins. Meniran and sambiloto herbs have the potential to increase the system potential to be developed as a supplement to treat COVID-19.

### 1. Introduction

In December 2019, there was a report of the Coronavirus from the city of Wuhan, Hubei province, China. This virus has become a pandemic that has spread throughout the world to this day. The name COVID-19 stands for coronavirus diseases 2019 or also known as SARS-Cov-2. While this research was being conducted, COVID-19 cases were increasing, reaching 96.2 million in the world, 977 thousand positive cases in Indonesia, and 13,599 thousand positive cases in South Sumatra. COVID-19 infection, both moderate and severe symptoms, can cause pneumonia with an opaque appearance that can be

detected on a chest CT scan, pulmonary edema, and accumulation of pleural fluid in the lungs. The genetic sequence of SARS-CoV-2 showed that COVID-19 belongs to the -coronavirus genus, with 79% nucleotide identity to SARS-CoV and 51.8% identity to MERS-CoV. Inoculation with SARS-CoV-2 of human airway epithelial cells in vitro caused a cytopathic effect and cessation of ciliary movement of respiratory epithelial cells, similar to the cytopathic effect observed in SARS-CoV infection.<sup>1</sup>

Indonesia is one of the countries with great biodiversity. No less than 30,000 species of plants

exist in the tropical forests of Indonesia. Of these, around 9,600 species are known to have medicinal properties, but not all of them are used optimally as herbal medicines. The use of herbs is as medicine in the form of steeping ingredients, herbs, standardized herbal medicines, and phytopharmaceuticals. Herbal medicine is a cultural heritage of the Indonesian people, which has been traditionally and for generations used to improve health status.<sup>2,3</sup> Various plants with health potential have been studied regarding their use in improving the body's health status, including triggering the body's immune power in dealing with COVID-19.

## 2. Benefits of Meniran (*Phyllanthus niruri* L.)

*Phyllanthus niruri* L. often called *meniran*, *didukung anak*, *daun gendong anak*, *gosau ma dung-dung*. This plant contains chemical tannins, resins, potassium, flavonoids (quercetin, quercitrin, isoquercitrin, astragalol, rutin; *kaemferol-4-ramnopyranoside*, *eridiktol-7-ramnopyranoside*), and lignans (cubebin dimethyl ether, urinatetralinurine, nirurine, phyllanthuric acid). hypophyllanthine, triterpene lup-20-en-3-ol. The leaves, roots, and all parts of this plant can be used empirically for the treatment of epilepsy, malaria, constipation, high blood pressure, irregular menstruation, thrush (leaves), heartburn, tooth pain (roots), poor urination, gonorrhoea, syphilis, kidney pain, diarrhoea, fever, tetanus, dirty blood, convulsions gagau, egg white in urine, urinary stones (all parts) and others.<sup>4</sup>

In testing the immunostimulant effect of meniran water extract in vivo using tilapia fish (*Oreochromis mossambicus*) at a dose range of 0.002 – 20 mg, it showed a significant increase in neutrophil activation and antibody response. Based on observations, fish with a test dose of 20 mg/kg BW showed a maximum increase in primary and secondary antibody responses, and a dose of 0.002 mg/kg showed higher neutrophil activation than the control group. The results of this test indicate that meniran extract has potential as an immunostimulant.<sup>5</sup>

Research in vitro using PBMC (peripheral blood

mononuclear cells) and macrophage cells of TB patients showed that aqueous extract of *Phyllanthus niruri* L. leaves had immunomodulatory with increased PBMC cell proliferation, increased phagocyte activity, and increased release of NO macrophages (dose-dependent effect). Clinical trials have also been carried out in a number of hospitals in Jakarta and Surabaya. It is reported that adjuvant therapy or complementary therapy is a drug that is consumed as a supporter of the main drug effect because it is known to increase the potency of the main drug. Meniran extracts succeeded in shortening the duration of treatment in several diseases such as TB, hepatitis, and candidiasis vaginalis. The addition of meniran extract to anti-tuberculosis drugs for post-primary can encourage changes in acid-fast bacilli (BTA) three times greater. The results of clinical testing showed that patients who received anti-tuberculosis drugs along with 50 mg of meniran extract, recovered at week 6 while patients who only received anti-tuberculosis drugs recovered at week 14. Furthermore, it was reported that there was no significant difference in side effects between the two treatments. In other words, giving meniran extract combined with standard anti-tuberculosis drugs was quite safe.<sup>6</sup>

Based on antiviral activity testing in mice, it was found that intraperitoneal administration of *Phyllanthus niruri* L. aqueous extract was effective in inhibiting Woodchuck hepatitis virus (WHV), in which 3 out of 4 test animals decreased and eliminated surface antigen titer and DNA polymerase activity in serum for 3-6 weeks, and no more WHV was detected at week 45 after previously discontinued administration at week 10.

Based on the tests carried out on mice, it was found that the administration of hexane extract, lignan-rich fraction, or phytertralin lignin Meniran orally provides consistent antioxidant effects against inflammatory agents in rat paws characterized by inhibition of the increase in IL-1 $\beta$ .

Based on the results of in vivo testing on mice (oxidative stress induced by nimesulide), it was found that the administration of aqueous extract had

antioxidant activity and protected the liver from damage caused by nimesulide by regulating oxidative stress in the liver. Administration Intraperitoneal showed more effective results than oral administration. Other tests in vivo showed the antioxidant activity of meniran water extract against paracetamol-induced liver damage in rats. The mechanism was through a decrease in glutamate oxaloacetate transaminase (GOT) and glutamate pyruvate transaminase. (GPT) serum, and increased catalase activity in the liver of the test group.

The use of meniran as a decoction, 15-30 g of meniran herb in 250 mL of water, taken 2-3 times per day. Dekokta is a liquid preparation made by extracting herbal preparations with water at a temperature of 90°C for 30 minutes. Meniran side effects in the form of hypoglycemia, hypotension, and electrolyte and mineral imbalances. Meniran can interact in the form of increasing the effectiveness of insulin and diabetes drugs if used together. Meniran contains geraniin reported to have negative inotropic, negative chronotropic, hypotensive, and ACE inhibitor effects. Therefore, it may enhance the effect of antihypertensive drugs  $\alpha$ -blockers and heart medication. Meniran herb ethanol extract can inhibit cytochrome P450 enzymes in vivo and in vitro. Meniran has a synergistic effect with antimicrobial drugs and antagonists with corticosteroids (immunosuppressant agents).

### **Benefits of Sambiloto (*Andrographis paniculata*)**

Sambiloto belongs to the *Andrographis* tribe *Acanthaceae*. The scientific name of the sambiloto medicinal plant is *Andrographis paniculata*. The popularity of the sambiloto plant in Indonesia has caused several regions/ethnicities in Indonesia to have different names, for example in Java it is known as Ki oray, ki peurat, takilo (Sundanese), bidara, sadilata, sambilata, takila (Javanese). While the name sambiloto in English is *green chireta*, *king of bitters*, while in Thailand it is called *fa thalaai*, in the Philippines it is called *aluy* and in France it is known as *roi des amers*. The chemical content of sambiloto

simplicia includes lactone terpenoids which include andrographolide, deoxyandrographolide, 11, 12-didehydro-14-deoxyandrographolide, neoandrographolide, andrographicide, deoxyandrographicide, and andropanoside. With andrographolide identity compounds. Sambiloto also contains chemical compounds of alkaloids, carbohydrates, resins, saponins, flavonoids, steroids, glycosides and tannins. The use of herbs described in the pharmacopoeia and certain official documents, namely: for bacillary dysentery, bronchitis, ulcers, colitis, coughs, dyspepsia, fever, hepatitis, malaria, mouth sores, wounds, tuberculosis, and venomous snakebites; In traditional medicine, it is used for colic, otitis media, vaginitis, pelvic inflammatory disease, chickenpox, eczema, and burns. This plant is used for tonsillitis, ulcers, typhoid, fever, itching, bitten by insects or poisonous snakes, diabetes, dysentery, ear inflammation, appendicitis, colds, and dirty blood.<sup>7</sup>

Sambiloto herb (*Andrographis paniculata* Burm. Nees) contains many components of chemical compounds that have been widely studied with activity as a hepatoprotection, and one of the active substances is *andrographolide*. The study aimed to determine the activity of *A. paniculata*, which has acted as an immunomodulator and hepatoprotection against Balb/c mice that had been induced by the hepatitis B vaccine. The three most active fractions of n-hexane showed an increase in the amount of IgG from the highest to the lowest, namely: F2 (containing groups of terpenoid compounds, steroids and flavonoids) IgG levels of 0.569 mg/20 g body weight in mice, F1 (containing groups of terpenoid compounds) IgG levels 0.126 mg/20 g BW of mice, F4 (containing groups of alkaloids and terpenoids) levels of IgG 0.094 mg/20 g BW of mice. Research has been carried out on the immunomodulatory effect of andrographolide on innate and adaptive immune responses using mice at a dose of 1 mg/kg. The results showed that there was a decrease in the production of anti-HBs antibodies and the number of splenocytes producing IL-4. Andrographolides can modulate innate and adaptive immune responses by regulating macrophage

phenotypic polarization and antibody Ag-specific<sup>8,9</sup>

A double-blind, randomized controlled trial of *A. paniculata* in patients with uncomplicated upper respiratory tract infection, with a total of 223 patients divided into two groups (placebo, and *A. paniculata* (200 mg/day)). From clinical research, it was shown that extract of *A. paniculata* is effective for reducing symptoms of upper respiratory tract infection, with effectiveness 2.1 times (52.7%) higher than placebo. An andrographolide clinical trial was conducted to examine 13 HIV-positive patients and five healthy volunteers who were HIV-negative. The study started with a dose of 5 mg/kg for the first 3 weeks, then increased to 10 mg/kg for 3 weeks, and then increased to 20 mg/kg for the last 3 weeks. Andrographolide administration significantly increased the CD4+ lymphocyte count from an initial mean of 405 to 501 in HIV-positive patients. There was no statistically significant change in the mean blood level of HIV-1 viral load. A recent study summarized that andrographolide derivatives might be promising candidates for preventing HIV infection, suggesting that andrographolides inhibit gp120-mediated fusion of HL2/3 cells with T2M-bl cells.<sup>10,11</sup>

Several studies have reported the antioxidant activity of *A. paniculata* and its constituents.<sup>9,10</sup> Aqueous extract of *A. paniculata* significantly increased the activity of antioxidant defense enzymes such as catalase, superoxide dismutase, and *glutathione-S-transferase* and reduced glutathione content. This extract significantly inhibited lipid peroxidation by lowering the levels of thiobarbituric acid reactive substances in the liver and kidneys of diabetic rats (compared to normal rats) and also significantly increased hepatic glutathione concentration levels. *Pre-treatment* of andrographolide was reported to significantly attenuate the accumulation of phorbol-12-myristate-13-acetate- (PMA-) induced ROS formation and N-formyl-methionyl-leucyl-phenylalanine- (fMLP-) that induces mouse neutrophil adhesion. It was shown that *in vivo* that administration of andrographolide sulfonate (using a water-soluble andrographolide),

intraperitoneally reduced the severity of colitis in 2-4 trinitrobenzene-induced rats (TNBS).<sup>12,13</sup>

Usage: 3-9 g of dried herbs or 25-75 g of fresh herbs as a single dose as needed. A total of three grams of dry ingredients or 25 grams of fresh ingredients are boiled and taken 2 times a day before eating. Undesirable effects of using high doses of sambiloto herbs can cause stomach discomfort, vomiting, nausea, and loss of appetite. This is due to the sambiloto taste of andrographolide, while in women, it can cause antifertility effects. It has been reported (very rarely) the occurrence of itching (chills/urticaria) and swelling of the eyes after drinking sambiloto stew. It is recommended to avoid this plant during pregnancy due to its ovulation prevention effect. Individuals who are allergic to plants can even develop anaphylactic reactions. Avoid long-term use concurrently with immunosuppressant drugs. Sambiloto herb extract may have a synergistic effect with isoniazid. Sambiloto has a hypotensive and antiplatelet effect, so it can increase the effect of antihypertensive and antiplatelet drugs.

## 2. Conclusion

Meniran and sambiloto herbs have the potential to increase the immune system potential to be developed as a supplement for the management of COVID-19.

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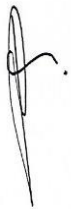


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**Letter of Acceptance**

Manuscript “Potential of Meniran (*Phyllanthus niruri L.*) and Sambiloto (*Andrographis paniculata*) as a Supplement to the Management of Coronavirus Disease 2019 (COVID-19)” by Rachmat Hidayat\*, Patricia Wulandari, has been accepted to publish in Eureka Herba Indonesia Vol 3 issue 2 in August 2022.

Cordially,



Prof. Paula Magnano, PhD

Editor



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## Potential of Meniran (*Phyllanthus niruri* L.) and Sambiloto (*Andrographis paniculata*) as a Supplement to the Management of Coronavirus Disease 2019 (COVID-19)

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### ABSTRACT

COVID-19 infection with moderate or severe symptoms can cause pneumonia with an opaque appearance that can be detected on a chest CT scan, pulmonary edema, and accumulation of pleural fluid in the lungs. The use of herbs as health drinks is thought to play a role in increasing the body's immunity. Meniran plant (*Phyllanthus niruri*) contains tannins and flavonoids, which are efficacious as immunomodulators. Meanwhile, sambiloto also contains chemical compounds of alkaloids, carbohydrates, resins, saponins, flavonoids, steroids, glycosides, and tannins. Meniran and sambiloto herbs have the potential to increase the system potential to be developed as a supplement to treat COVID-19.

### 1. Introduction

In December 2019, there was a report of the Coronavirus from the city of Wuhan, Hubei province, China. This virus has become a pandemic that has spread throughout the world to this day. The name COVID-19 stands for coronavirus diseases 2019 or also known as SARS-CoV-2. While this research was being conducted, COVID-19 cases were increasing, reaching 96.2 million in the world, 977 thousand positive cases in Indonesia, and 13,599 thousand positive cases in South Sumatra. COVID-19 infection, both moderate and severe symptoms, can cause pneumonia with an opaque appearance that can be

detected on a chest CT scan, pulmonary edema, and accumulation of pleural fluid in the lungs. The genetic sequence of SARS-CoV-2 showed that COVID-19 belongs to the -coronavirus genus, with 79% nucleotide identity to SARS-CoV and 51.8% identity to MERS-CoV. Inoculation with SARS-CoV-2 of human airway epithelial cells in vitro caused a cytopathic effect and cessation of ciliary movement of respiratory epithelial cells, similar to the cytopathic effect observed in SARS-CoV infection.<sup>1</sup>

Indonesia is one of the countries with great biodiversity. No less than 30,000 species of plants

**Galley Proof**

exist in the tropical forests of Indonesia. Of these, around 9,600 species are known to have medicinal properties, but not all of them are used optimally as herbal medicines. The use of herbs is as medicine in the form of steeping ingredients, herbs, standardized herbal medicines, and phytopharmaceuticals. Herbal medicine is a cultural heritage of the Indonesian people, which has been traditionally and for generations used to improve health status.<sup>2,3</sup> Various plants with health potential have been studied regarding their use in improving the body's health status, including triggering the body's immune power in dealing with COVID-19.

## 2. Benefits of Meniran (*Phyllanthus niruri* L.)

*Phyllanthus niruri* L. often called *meniran*, *didukung anak*, *daun gendong anak*, *gosau ma dung-dung*. This plant contains chemical tannins, resins, potassium, flavonoids (quercetin, quercitrin, isoquercitrin, astragaln, rutin; *kaemferol-4-ramnopyranoside*, *eridiktol-7-ramnopyranoside*), and lignans (cubebin dimethyl ether, urinatetralinurine, nirurine phylaniruricide). hypophilanthine, triperpenylpiperonyl (10-en-3-ol). The leaves, roots, and all parts of this plant can be used empirically for the treatment of epilepsy, malaria, constipation, high blood pressure, irregular menstruation, thrush (leaves), heartburn, tooth pain (roots), poor urination, gonorrhea, syphilis, kidney pain, diarrhea, fever, tetanus, dirty blood, convulsions gagau, egg white in urine, urinary stones (all parts) and others.<sup>4</sup>

In testing the immunostimulant effect of meniran water extract in vivo using tilapia fish (*Oreochromis mossambicus*) at a dose range of 0.002 – 20 mg, it showed a significant increase in neutrophil activation and antibody response. Based on observations, fish with a test dose of 20 mg/kg BW showed a maximum increase in primary and secondary antibody responses, and a dose of 0.002 mg/kg showed higher neutrophil activation than the control group. The results of this test indicate that meniran extract has potential as an immunostimulant.<sup>5</sup>

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Based on antiviral activity testing in mice, it was found that intraperitoneal administration of *Phyllanthus niruri* L. aqueous extract was effective in inhibiting Woodchuck hepatitis virus (WHV), in which 3 out of 4 test animals decreased and eliminated surface antigen titer and DNA polymerase activity in serum for 3-6 weeks, and no more WHV was detected at week 45 after previously discontinued administration at week 10.

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#### **Benefits of Sambiloto (*Andrographis paniculata*)**

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Usage: 3-9 g of dried herbs or 25-75 g of fresh herbs as a single dose as needed. A total of three grams of dry ingredients or 25 grams of fresh ingredients are boiled and taken 2 times a day before eating. Undesirable effects of using high doses of sambiloto herbs can cause stomach discomfort, vomiting, nausea, and loss of appetite. This is due to the sambiloto taste of andrographolide, while in women, it can cause antifertility effects. It has been reported (very rarely) the occurrence of itching (chills/urticaria) and swelling of the eyes after drinking sambiloto stew. It is recommended to avoid this plant during pregnancy due to its ovulation prevention effect. Individuals who are allergic to plants can even develop anaphylactic reactions. Avoid long-term use concurrently with immunosuppressant drugs. Sambiloto herb extract may have a synergistic effect with isoniazid. Sambiloto has a hypotensive and antiplatelet effect, so it can increase the effect of antihypertensive and antiplatelet drugs.

## 2. Conclusion

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# CERTIFICATE

O F P U B L I C A T I O N

Potential of Meniran (*Phyllanthus niruri* L.) and Sambiloto (*Andrographis paniculata*) as a Supplement to the Management of Coronavirus Disease 2019 (COVID-19)

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