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Overview of Phytochemicals and Pharmacological Activities of Sungkai (*Peronema canescens* Jack): Popular Plants in Indonesia during the Covid-19 Pandemic

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Abstract :
Background: *Sungkai (Peronema canescens) is one of the most popular medicinal plants used widely by Indonesian people during the COVID-19 Pandemic. This plant is commonly grown in tropical areas such as Indonesia, Thailand, and Malaysia. Empirically, P.canescens leaves are used by the community to treat fever, colds, malaria, intestinal worms, bruises, herbs for women after childbirth, and maintain a healthy body.*
Methods: *This article summarizes the phytochemical compounds in P.canescens and their pharmacological activity based on the literature obtained from databases such as PubMed, ProQuest, ScienceDirect, and Google Scholar. The summarized articles were articles published in the last ten years.*
Results*: Twenty-two papers containing the phytochemical and pharmacological activity of P.canescens were obtained.*
Conclusion: *The secondary metabolites in P.canescens were alkaloid, flavonoid, terpenoid, steroid, phenolic, saponin, and tannin. The pharmacological activity of P.canescens was anticancer, antimicrobial, antimalarial, antioxidant, anti-tyrosinase, immunostimulant, antidiabetic, antipyretic, antihyperuricemic, and anti-inflammatory.*
Keywords: *covid-19, immunostimulant, phytochemistry, pharmacology, sungkai*

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I. INTRODUCTION

Peronema canescens (**figure 1**), called *sungkai* in Indonesia, belongs to the *Verbenaceae* family and is widely found in Thailand, Indonesia, Malaysia, and Singapore [1]. In the Serawai tribe, leaves of *P.canescens* are pounded and patched for bruising. In the Lembak tribe, steeping *P.canescens* leaves are used to reduce fever, treat malaria and maintain a healthy body. The Dayak tribe in East Kalimantan still maintains ancestral traditions by using the surrounding plants for treatment or health. For example, the plant *P.canescens* with young leaves is used as fever, cold, worm medicine, and for women after childbirth [3].

Currently, the whole world is still experiencing the COVID-19 Pandemic. The World Health Organization (WHO) has issued signs and symptoms of Covid-19, including coughing, flu, shortness of breath, fatigue, dizziness, nausea, and vomiting. A patient infected with the COVID-19 virus continues to grow. Globally as of December 29, 2021, WHO reported 281.808.270 confirmed cases of COVID-19, including 5.411.759 deaths.

Regarding the COVID-19 Pandemic that has occurred worldwide, including Indonesia, for the last 2 (two) years, *P.canescens* used as traditional medicine as an anti-COVID-19 drug because it was believed to help relieve symptoms due to the COVID-19 virus due to conditions in certain areas that have limited access to health. Like people in East Kalimantan Province, they have also used *P.canescens* as a traditional medicine to treat diseases caused by the COVID-19 virus. Conventional medicine is safer than modern medicine because conventional medicine has relatively fewer side effects than modern medicine. However, it is still necessary to use traditional medicine to minimize its side effects, namely the correctness of the drug, the accuracy of the dose, the timeliness of use, the accuracy of how to use it, not being misused, and the accuracy of selecting drugs for specific diseases [4].

P.canescens is a herbal plant that is the most widely used to modulate the immune system in dealing with the COVID-19 virus. Over time, many countries have succeeded in being preventive and curative. Based on this, the authors are interested in conducting a literature study on the phytochemical content and pharmacological activity of *P.canescens*.

Figure no 1. Sungkai (*Peronema canescens*)

II. METHODS

The articles used in this review were searched from scientific literature databases, i.e., PubMed, ScienceDirect, ProQuest, and Google Scholar. It was published in the last ten years, from 2011 to 2021. **Figure 2** shows a flow chart of the selection of the articles reviewed.

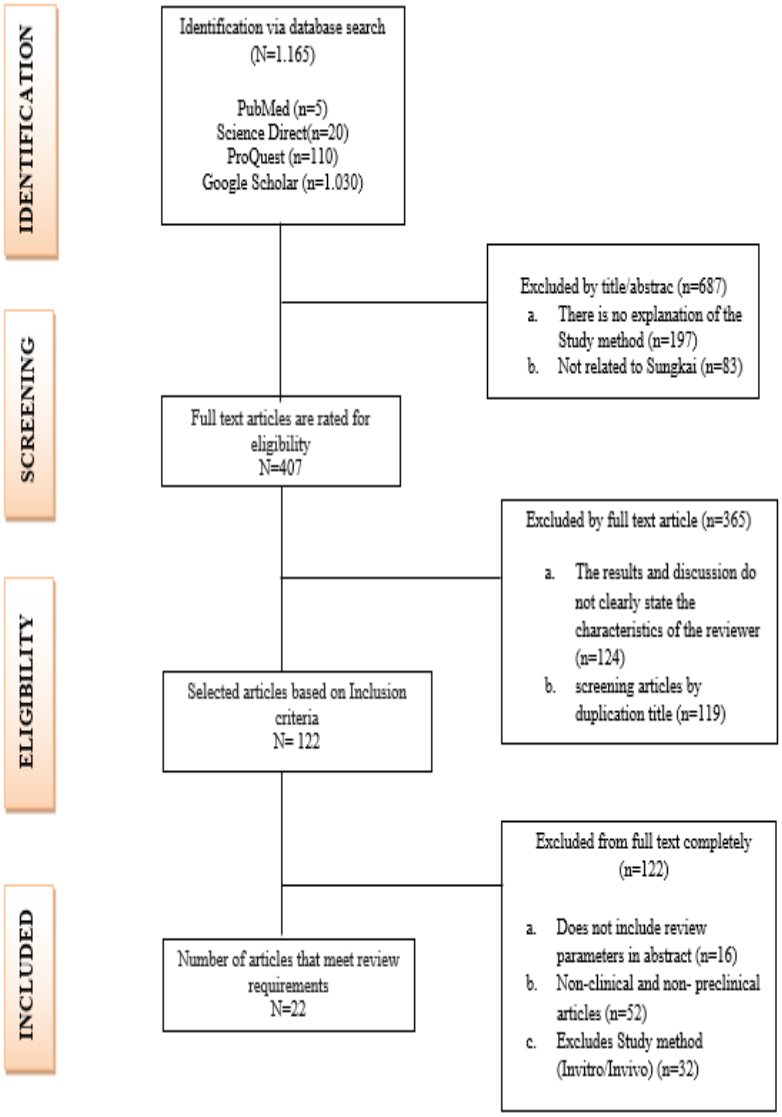

Figure no 2. Systematic search flowchart

III. RESULT AND DISCUSSION

The literature study on phytochemicals and pharmacological activities *P.canescens* used 22 articles, of which 13 pieces were on the phytochemicals of *P.canescens,* and 22 papers were on pharmacological activities.

PHYTOCHEMISTRY

Phytochemical screening is a method used to study the components of active compounds in samples by identifying the content of secondary metabolites using specific chemical reagents. The reaction is declared positive, containing certain secondary metabolite compounds if there is a color change in the study solution when the reagent is added or precipitation [5]. The leaves of *P.canescens* contain many secondary metabolites, based on the following discussion reviewed from various articles.

Table no 1: Phytochemical results of *P.canescens*

No	SAMPLE	Phytochemical Content							Ref.
		Alkaloid	Flavonoids	Terpenoids	Steroid	Phenolic	Saponins	Tannins	
1.	Ethanol extract	✓	✓			✓	✓	✓	[6]
2.	Ethanol extract	✓	✓	✓	✓	✓	✓	✓	[7]
3.	Ethanol extract	✓	✓	✓	✓	✓	✓	✓	[8]
4.	Leaf extract		✓	✓	✓				[9]
5.	Leaf extract		✓			✓		\	[10]
6.	Ethyl acetate fraction	✓	✓			✓		✓	[12]
7.	Infusion leaf	✓	✓	✓		✓	✓	✓	[13]
8.	Leaf extract	✓	✓	✓		✓	✓		[14]
9.	Ethanol extract	✓	✓			✓	✓		[15]
10.	Endophytic fungi isolate	✓	✓	✓		✓			[16]
11.	Ethanol extract	✓	✓		✓	✓	✓	✓	[17]
12.	Leaf extract			✓					[18]
13.	Extract n-butanol	✓	✓	✓		✓	✓	✓	[19]

Based on the study by *Latief et al.*, the results of a phytochemical screening study, ethanol extract of *P.canescens* leaves contain phenols, flavonoids, tannins, alkaloids, and saponins [6]. The study by *Latief et al.* showed that the ethanolic extract of *P.canescens* leaves contained alkaloids, flavonoids, saponins, steroids, triterpenoids, phenolics, and tannins [7]. Phytochemical screening study by *Prasiwi* for the ethanol fraction of *P.canescens* leaves contain flavonoids, saponins, tannins, steroids, terpenoids, alkaloids, and phenol [8]. In the phytochemical screening study by *Yani et al., P.canescens* leaf extract contains chemical compounds of peronemin, sitosterol, isopropanol, phytol, terpenoids, and flavonoid [9]. Based on *Yohandini* et al., the spectrophotometric analysis showed that leaf extract *P.canescens* contains flavonoid and phenolic compounds [10]. Gas Chromatography and Mass Spectroscopy (GC-MS) characterization, also carried out by *Neli et al.*, obtained the components of chemical compounds in the ethyl acetate fraction of *P.canescens* leaves. Only dominantly contains a group of fatty acid compounds consisting of *decanoic acid, dodecanoic acid, tetradecanoic acid, methyl 11-octadecenoate, and 1,2-benzene dicarboxylic.* Alkane compounds consist of *heptacosane* and *tetracontane.* The alcohol compounds consist of *isopropyl myristate, 1–policosanol, and 1–hexadecanol* [11].

Based on the study by *Ramadenti et al.,* the phytochemical screening study results on the ethyl acetate fraction of *P.canescens* leaves showed the presence of secondary metabolites alkaloids, flavonoids, tannins, and phenolics [12]. Study results by *Rahman et al. The* phytochemical screening study of *P.canescens* leaf infusion contained secondary metabolites of phenol, tannins, saponins, flavonoids, alkaloids, and terpenoids [13]. Study

results by *Dillasamola et al.* the phytochemical screening study of *P.canescens* leaf extract containing flavonoids, alkaloids, saponins, phenolics, and terpenoids [14]. The results of the study by *Dillasamola* on screening study for ethanol extract of *P.canescens* leaves showed that it contains flavonoids, alkaloids, saponins, and phenols [15]. The study by *Ibrahim et al*. investigated secondary metabolites in isolates of endophytic fungus *P.canescens* leaves are alkaloids, terpenoids, flavonoids, and polyphenols [16]. Study results by *Latief et al*. phytochemical screening study of ethanol extract of *P.canescens* leaves containing alkaloids, flavonoids, steroids, phenols, saponins, and tannins [17]. In the study by *Fareez et al., P.canescens* leaves extract contains the active compound Peronemin, a class of terpenoid compounds [18]. The results of a study by *Maulana et al., the* phytochemical screening study of the n-butanol extract of *P.canescens leaves* containing alkaloids, flavonoids, terpenoids, phenols, saponins, and tannins [19].

PHARMACOLOGICAL ACTIVITY

Anticancer

Based on the study by *Ahmad & Ibrahim*, It has been known that the methanol extract and the n-hexane fraction of *P.canescens leaves* have cytotoxic pharmacological activity against shrimp larvae (*Artemia salina Leach*) study animals. The study was carried out using the Brine Shrimp Lethality Study (BSLT) method on *A. salina leach.* The concentration for each extract was different for the methanol extract, 50, 200, 400, 800, and 1000 ppm. The study results showed that 50% of the animals died at 200-400 ppm concentrations. The concentration of n-hexane fraction was 10, 50, 100, 200, and 400 ppm. Reed and Muench's study showed that the extract methanol and n-hexane fraction leaf of *P.canescens* killed 50% of *A. salina leach* study animals which LC_{50} value of methanol extract was 387.257 and n-hexane was 107.399 ppm. *A. salina* death mechanism related to the function of secondary metabolite compounds alkaloids, saponins, phenolic compounds, steroids, terpenoids, and tannins, which can inhibit larval feeding power (antifeedant). The compound acts as a stomach poison. These compounds enter the body of the larvae so that the digestive system will be disturbed. This compound can also inhibit taste receptors in the mouth area of the larvae, so the larvae cannot recognize their food [20].

In another study by *Abraham & Siswandono*, chloroform extract of *P.canescens* leaf has anticancer activity on colon cancer cells HT-29 and primary adenocarcinoma (AdenoCa pT3N1cM1). The cytotoxicity was measured using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) and flow cytometry assay. Cell suspension HT-29 and AdenoCa pT3N1cM1 with a density of 1 x 10^6 cells/100 µL was treated by extract concentration 1.563, 3.125, 6.25, 12.5, 25.0, 50.0, 100.0 and 200.0 µg/mL for 24 hours. The results showed that against AdenoCa cells, the cytotoxicity value (IC_{50}) was 1.897 µg/mL. The inhibitory action of the extract in the synthesis and mitotic phases of the cell cycle showed that different concentrations inhibit HT-29 (293614 µg/mL) by 26.79% and 0.16%, and AdenoCa cells (14.807 µg/mL) by 10.27% and 19.29%. Induced apoptotic activity on HT-29 (29.614 µg/mL) and AdenoCa cells (14.807 µg/mL) was 26.58% and 11.50%. HT-29 and AdenoCa cells necrosis activity was 0.02% and 9.56%, respectively. This study confirmed that the *P.canescens* extract had anticancer effects in primary colon cancer cells HT-29 and AdenoCa pT3N1cM1 cells. It could suppress cell growth, cell cycle arrest, apoptosis, and necrosis [21].

The following study by *Suwandi et al.* showed that acetone, ethanol, and aqueous extracts of *P.canescens leaves* with concentrations of 0.02 and 0.04 g/mL, respectively, had cytotoxic activity against Vero cells using MTT assay. ELISA analyzed it at 595 nm, which IC_{50} for acetone, ethanol, and aqueous extract were 23.37±5.63, 629.46±24.85, and 634.00±144.82 µg/mL, respectively. Acetone extract at the highest concentration, 400 µg/mL, was highly cytotoxic, causing the death of 98.26±0.67% of Vero cells. 200 µg/mL concentration caused the death of 99.10±1.56% of cells. In contrast, at the same highest concentration, 400 µg/mL, ethanol and aqueous extract resulted in only 11.34±6.38% and 8.69±6.32% mortality of Vero cells, respectively. IC_{50} values for acetone, ethanol, and aqueous extract were 23.37 ±5.63, 629.46±24.85, and 634.00±144.82 µg/mL, respectively. Statistical analysis showed a significant difference between the three extracts [22].

Chemotherapy and radiotherapy can cause the marrow bone to stop producing white blood cells, essential for infection protection. As a result, the cancer patient's body will experience a loss of power, and her body will be incapable of defending itself against infection with the COVID-19 virus [23]. Some people will be infected with the COVID-19 virus without having any symptoms, while others will develop mild, moderate, or severe COVID-19 symptoms. Symptom light is similar to the common cold that persons with ordinary system immunity encounter. It was different for cancer patients, as their symptoms were more severe, such as high fever, chest pain, blue lips and visible nails, and shortness of breath till they dropped [24].

Antimicrobial

Antibacterial activity based on a study by *Ibrahim et al.*, the study was carried out using the solid diffusion method using a concentration of 4% against four types of bacteria, *Escherichia coli*, *Salmonella*

typhosa, Staphylococcus aureus, and *Bacillus subtilis*. Ethanol fraction *P.canescens* leaves concentration 4% formulated into gel dosage. The study results showed that the gel dosage of *P.canescens* leaves was active as antiseptic to *E.coli*, *S.typhosa, S.aureus*, and *B.subtilis* with inhibition zone 12.03, 5.25, 6.78, and 6.00 [25].

The activity was suspected given by the ability of the ethanol extract fraction to kill the study microbes of the secondary metabolites contained in the extract. The secondary metabolites in *P.canescens leaves* are polyphenols: flavonoids and tannins [26]. Mechanism antibacterial group secondary metabolites polyphenolic compounds are the largest group in plants, one of which is tannins which have antibacterial activity. The estimated mechanism is that the toxicity of the polyphenolic group of compounds can damage bacterial cell membranes. The antibacterial mechanism by the flavonoid group was forming complex compounds against extracellular proteins that disrupt the integrity of the bacterial cell membrane [27].

The next study by *Fransiska et al.* showed that ethanol extract of *P.canescens* leaf has antibacterial pharmacological activity in *E.coli.* The Kirby-Bauer disc method was used in this study. The concentration extract was 25%, 50%, 75%, and 100%. Colonies of *E.coli* grown in petri dishes containing *Muller Hinton Agar* (MHA) were treated by placing Kirby-Bauer disc paper which had previously been soaked in *P.canescens* leaf extract, for 15 minutes and then incubated for 24 hours at temperature 37°C. After 24 hours of incubation, the diameter of the inhibition zone formed was determined. Extract could inhibit *E.coli* growth whose inhibition zone was 3.75, 3.5, 3.5, and 7.75 mm for concentration of 25%, 50%, 75% and 100%. Based on the study, a concentration of 25% more effectively inhibits the growth of *E.coli* [28].

The inhibition zones at each concentration are formed due to the active compounds possessed by *P.canescens* leaves, such as flavonoids, saponins, and tannins. These compounds have an activity that can be used as antibacterial [29]. Another compound is tannin, which thwarts the formation of bacterial cells by blocking the action of DNA topoisomerase and reverse transcriptase enzyme. Microbial cell adhesion was inhibited, enzymes were deactivated, and protein transport was disrupted in the inner layer of cells. The cell wall was formed imperfectly because the polypeptides owned by the cell wall are damaged, so bacterial cells become lysed and die due to osmotic and physical pressure [30].

Another study by *Yohandini et al.* showed that n-hexane extract, ethyl acetate extract, and *P.canescens* leaf methanol extract *had* antibacterial activity (*E.coli, S.aureus,* and *S.typhii*). The study was carried out by disc diffusion method using disc paper with a diameter of 6 mm with sample concentrations of 4%, 2%, 1%, and 0.5 %. Disc paper was dipped in the sample then placed on nutrient agar (NA) media that had been inoculated with *E.coli, S.aureus,* and *S.typhii* bacteria. Incubate at 37°C for 24 hours. Observations were made based on the formation of inhibition zones around the paper discs. The results showed that the antibacterial activity of all extracts had an inhibitory zone diameter ranging from 7.7±0.19, 1±0.4 mm at study concentrations of 500-4000 g/mL. However, at several study concentrations, difference concentration did not give a significant difference in the value of the diameter of the inhibition zone. The antibacterial activity of methanol extract was lower than that of ethyl acetate and n-hexane extracts [10].

Antibacterial activity was classified as an intense activity if the diameter of the inhibition zone was 10-20 mm, moderate activity if the resistance was 5-10 against the three study bacteria up to the study concentration of 500 g /mL. The antibacterial activity of *P.canescens* extract was thought to be related to the chemical content of flavonoids and phenolics [31]. Bacteria and viruses together can result in somebody experiencing disease infection at once. However, it was difficult to recognize the difference in diseases caused by viruses or bacteria, such as meningitis, diarrhea, and pneumonia. Besides, that hurts the throat and enters the list of conditions caused by viruses or bacteria. Sick throat is not a disease but symptoms when experiencing illness-specific symptoms. Types of viruses that cause flu and colds are the same as COVID-19; they can result in the sick throat, flu symptoms, and cough.

Table no. 2: Pharmacological Activity of *P.canescens*

Activity	*Part of the plant used*	*Dosage / Concentration*	*Study methods*	*Animal, cell/or specimen used*	*Type of extract/formulation*	*Results*	*Region*	*Reff*
Anticancer	Leaf	- 50, 200, 400, 800, and 1000 ppm (methanol extract) - 10, 50, 100, 200, and 400 ppm (n-hexane fraction)	Brine shrimp lethality study (BSLT)	Shrimp larvae (*Artemia salina Leach)*	Methanol extract and n-hexane fraction	LC50 was 387.257 ppm (methanol extract) and 107.399 ppm (n-hexane fraction)	Indonesia	[20]
	Leaf	1.563, 3.125, 6.25, 12.5, 25.0, 50.0, 100.0 and 200.0 g/mL	MTT and flow cytometry assay	Colon cancer cells (HT-29 and AdenoCa pT3N1cM1)	Extract chloroform	*P.canescens* suppresses cell growth, cell cycle arrest, apoptosis, and necrosis.	Indonesia	[21]
	Leaf	200 and 400 g/mL	MTT assay	Vero cell	Acetone, ethanol, and water extracts	IC_{50} values for acetone, ethanol, and aqueous extract were 23.37 ±5.63, 629.46±24.85, and 634.00±144.82 µg/mL	Indonesia	[22]
Antimicrobial	Leaf	4%	Solid Diffusion Study	*E.coli, S.typhosa, S.aureus* and *B.subtilis.*	Ethanol Extract	Concentration of 4% active against *Staphylococcus aureus, Salmonella thyposa, Escherichia coli* and *Bacillus subtilis.*	Indonesia	[25]
	Leaf	25%, 50%, 75% and 100%	Kirby-Bauer disc method	*E.coli*	Ethanol extract	The concentration of 25% effectively inhibits the growth of *E.coli*	Indonesia	[28]
	Leaf	500, 1000, 2000 and 4000 g/mL	Disc diffusion method	*E.coli, S.aureus,* and *Salmonella typhi*	Methanol, ethyl acetate, and n-hexane extracts of	The antibacterial activity of methanol extract was lower than that of ethyl acetate and n-hexane extracts.	Indonesia	[10]
Antimalarial	Leaf	0.028, 0.056 and 0.084 g/kg BW	Mice were infected with *Plasmodium berghei*	Male mice *(Mus musculus)*	Extract n-hexane	Extract inhibited parasitemia	Indonesia	[32]
	Leaf	0.028, 0.056 and 0.0084 g/kg BW	Mice were infected with *P.berghei*	Male mice *(Mus musculus)*	Ethyl acetate fraction	A dose of 0.056 g/kg BW can inhibit the growth of parasitemia by 50.89 %.	Indonesia	[12]
	Leaf	50, 100, 150, and 200%.	MTT assay	Plasmodium falciparum strains D10 and FCR3	Acetone, ethanol, and aqueous extract	The aqueous extract was more effective as antiplasmodial	Indonesia	[22]
	Leaf	0.028, 0.056 and 0.0084 g/kg BW	Mice were infected with *P.berghei*	Male mice *(Mus musculus)*	Ethanol fraction	A dose of 0.084g/kg BW has the potential as an antimalarial with a percentage of 54.06%	Indonesia	[8]
Antioxidant	Leaf	- Ethanol extract 10, 30, 50, and 70 ppm. - Fraction n-hexane 100, 200, 300, 400, and 500 ppm. - Ethyl acetate fraction 1, 5,10,15 and 20 ppm.	DPPH method	1,1-diphenyl-2picrylhydrazyl (DPPH)	Ethanol extract, n-hexane fraction, and ethyl acetate fraction	Each extract had antioxidant activity	Indonesia	[11]
	Leaf	5000 ppm	Sprayed with 0.01% DPPH solution.	Solution of DPPH 0.01%	n-butanol fraction	Fraction had antioxidant activity	Indonesia	[19]
	Leaf	50, 100, 200, 300, 500 and 1000 g/mL	DPPH method	Solution of DPPH 0.01%	Methanol, ethyl acetate and n-hexane extracts	Ethyl acetate extract was classified as a moderate antioxidant, while the other two extracts were not active.	Indonesia	[10]
Antityrosinase	Leaf	5000 ppm	Solution of the tyrosinase enzyme and L-DOPA	Solution tyrosinase	n-butanol fraction	Tyrosinase inhibition	Indonesia	[19]
Immunomodulator	Leaf	0.186mg/kg BW, 0.375mg/kg BW, and 0.5625 mg/kg BW	- Treatment with one gavage, during the day, with a span of 24 hours. - Leukocyte count	Male mice *(Mus musculus)*	Leaf extract	A dose of 0.5625 mg/kg BW increased the number of leukocytes by 36%.	Indonesia	[29]
	Leaf	5%,15%, and 20%/30 gBB	Carbon clearance study	Male mice (*Mus musculus*)	Infusion	Concentration of 20% / 30 g BB produced more leukocytes.	Indonesia	[38]

	Leaf	10, 50, 100 and 200 mg/kg BW	Carbon clearance	Male mice *(Mus musculus)*	Ethanol extract	The highest phagocytic index was obtained at a dose of 200 mg/kg BW	Indonesia	[14]
	Leaf	10, 50, 100 and 200 mg/kg BW	Carbon clearance	Male mice *(mus musculus)*	Ethanol extract	A 200 mg/kg BW dose showed the highest number of leukocytes.	Indonesia	[15]
Antidiabetes	Leaf	175, 350 and 700 mg/kg BW	Induction with alloxan at a dose of 150 mg/kg BW	Male mice *(Mus musculus*	Ethanol extract	A dose of 350 mg/kg BW has the optimal potential to lower blood glucose levels.	Indonesia	[42]
Antipyretic	Leaf	0.186, 0.37 and 0.5625 mg/kg BW	Fever induction DPT-HB	Male mice *(Mus musculus*	Leaf extract	A dose of 0.5625 can reduce body temperature 29%, better than paracetamol only 26%	Indonesia	[29]
	Leaf	10%, 20% and 30%	Induction with 5% peptone, according to the bodyweight of each mouse subcutaneously.	Male Mice (*Mus musculus*)	Infusion	10% and 20% doses reduce the body temperature of mice more effectively.	Indonesia	[47]
Antihyperuricemia (Gout)	Leaf	125, 250 and 500 mg/kg BW	Induction of potassium oxonate 250 mg/kg BW intraperitoneally and chicken liver juice 2mL/200grBW orally	Male mice *(mus musculus)*	Ethanol extract	The dose of 500 Mg/kg BW reduced uric acid levels by 38.66%.	Indonesia	[48]
AntiInflammatory (Inflammation)	Leaf	5, 10, and 1 5%	Carrageenan induction	Male mice *(mus musculus)*	Ethanol extract	A dose of 15% has Anti-inflammatory activity reaching 50% inhibition.	Indonesia	[17]

Antimalarial

P.canescens is an antimalarial drug that reduces parasitemia in the blood of infected *M.musculus* with *P.berghei*. *P.canescens* was thought to have potential as an antimalarial because of its secondary metabolite content potential as antiplasmodial in infected *M.musculus.* Based on *Andriyani et al.,* the n-hexane extract of *P.canescens leaves* showed antimalarial activity in *M.musculus* study animals. The study was conducted by hearing how *M.musculus* was first infected with *P.berghei* and then given the n-hexane fraction of *P.canescens* leaves orally with doses of 0.028, 0.056, and 0.084 g/kg BW, respectively. Based on the study and data analysis that has been done, the results showed that a dose of 0.028 g/kg BW was able to inhibit parasitemia by 33.49%, an amount of 0.056 g/kg BW by 57.91%, and a dose of 0.084 g/kg BW by 61.69%. from these results it can be concluded that the higher the amount is given, the higher the percent inhibition [32].

Another study by *Ramadenti et al.* showed that the ethyl acetate fraction of *P. canescens* leaves had pharmacological activity as antiplasmodial, which was studied on *M.musculus* infected with *P.berghei* by giving doses of 0.028, 0.056, and 0.084 g/kg BW. Parasitemia was calculated by taking a blood sample from the tail *M. musculus* to make blood preparations observed under a microscope. If the development of parasitemia in the blood has reached 20-30%, then *M. musculus* can be given treatment. The results showed that a dose of 0.056 g/kg BW could reduce parasitemia in the blood well up to the seventh day of observation. It means that parasitemia is not resistant to drugs, so its growth will decrease. The statistical analysis showed different activity of antiplasmodial and a higher percentage of parasitemia inhibition compared to positive and negative control groups [12].

A study conducted by *Suwandi et al.* extracts of acetone, ethanol, and leaf water of *P.canescens* with concentrations of 50, 100, 150, and 200% showed antiplasmodial activity. Against *P. falciparum* strains D10 and FCR3. The study results obtained, LC_{50} extracts were 26.33±1.65, 37.96±8.17, and 12.26±1.05 g/mL, respectively. *P. falciparum* strains D10 and 51.14±8.65, 70.22±14.13, and 34.85±6.04 g/mL, respectively, against strain FCR3. A selectivity index value of the respective extracts were 0.89, 16.46, and 51.70 for the D10 strain and 0.46, 8.90, and 18.00, respectively, for the FCR3 strain. The highest concentrations of acetone, ethanol, and aqueous extract inhibited the growth of the FCR3 strain by 90.51±2.32%, 92.76±0.43%, and 69.60±1.21%, respectively. The mean IC_{50} values for acetone, ethanol, and aqueous extracts were 51.14 ± 8.65, $_{70.22}$ ± 14.13, and 34.85 ± 6.04 g/mL, respectively. Statistical analysis showed that FCR3 revealed a significant difference between the three extracts. There was a significant difference between the ethanol extract and water. Still, there was no significant difference between acetone and ethanol extract or between acetone and aqueous extract. *P.canescens* leaf extract has good antiplasmodial activity against *P.falciparum* strain D10. However, activity against *P.falciparum* strain FCR3 was only proven with aqueous extracts because acetone and ethanol extracts showed poor antiplasmodial activity. Because of that, the aqueous leaf extract was more effective at showing better antiplasmodial activity than the acetone and ethanol extracts [22].

Another study conducted by *Prasiwi et al.* extracts the ethanolic fraction of *P.canescens leaves* also showed antiplasmodial activity against *P.berghei.* The study was carried out on *M. musculus,* the negative control group of mice infected with *P. berghei* was given distilled water, the positive control group of mice infected with *P. berghei* was given chloroquine at a *musculus* better than the synthetic drug chloroquine [8]. Malaria and COVID-19 almost have similar mechanism work diseases and appear to have potential. People infected with the malaria virus and time on endemics are at greater risk of suffering from COVID-19 because of

the side effects of the second disease [33]. Malaria and COVID-19 are caused by parasites, namely viruses, caused by low immunity until the virus can easily infect the body.

Antioxidants

A study conducted by *Pindan et al.* showed that the crude extract of the n-hexane fraction, ethyl acetate fraction, and ethanol fraction of *P.canescens* has antioxidant activity with IC_{50} (inhibitor concentration) values 29.549 ppm, 607.475 ppm, 12.986 ppm, and 15,766 ppm, respectively. The antioxidant activity was studied at various concentrations of the crude ethanol extract of 10, 30, 50, and 70 ppm. The n-hexane fractions were 100, 200, 300, 400, and 500 ppm. The ethyl acetate fraction and the remaining ethanol fraction were 1, 5, 10, 15, and 20 ppm. Quercetin as a comparison solution used a concentration variation of 0.5, 1, 2, and 4 ppm, respectively. The calculation of antioxidant activity can be seen from the color change of DPPH, which is expressed in percentage reduction [11].

It is determined to be used for the results of the DPPH study. Based on the percentage damping obtained, the IC_{50} value. IC_{50} rated can be identified as the amount of concentration that can inhibit free radical activity as much as 50%, namely the smaller the IC_{50} value, the greater the antioxidant activity. The greater the attention of the sample extract, the value of % antioxidant activity increases, as indicated by the lower IC_{50} value [11].

Suppose the compound is a powerful antioxidant of the value IC50< 10 ppm. If the value IC_{50} 10-50 ppm is a potent antioxidant, IC_{50} 50-100 ppm is a moderate antioxidant, IC_{50} 50-100 ppm is moderate, and IC_{50} 100-250 ppm is a weak antioxidant. From the results of the IC_{50} value, it was known that the crude extract, the ethyl acetate fraction, and the residual ethanol fraction have a solid antioxidant level, where the smaller the IC_{50} value, the higher the level of antioxidant activity of a sample [34].

A study conducted by *Putra. et al.* showed that the n-butanol fraction of *P.canescens leaves* at a concentration of 5000 ppm sample concentration had an antioxidant activity based on a qualitative study using the TLC method, marked by a pale yellow stain after being sprayed with 0.01% DPPH solution. Positive results have antioxidant activity indicated by yellow spots on the TLC plate [19].

Subsequent studies by *Yohandini et al.* showed that n-hexane extract, ethyl acetate extract, and *P.canescens* leaf methanol extract had antioxidant activity determined using the DPPH method with 50, 100, 200, 300, 500, and 1000 g/mL. The study results showed that the higher the study concentration, the greater the value of antioxidant activity obtained. The results of the p study at a concentration of 1000 g/mL, the percentage of inhibition of the ethyl acetate extract had the highest value, namely 76.14±6.20, compared to n-hexane extract only 40.90±3.40 and methanol extract 42.26±1.96. The IC_{50} 50% DPPH value results showed that the ethyl acetate extract had the smallest IC_{50} value of 320 compared to the n-hexane extract of 1567 and the methanol extract of 1281 [10].

An extract is categorized as a strong antioxidant if it has an IC_{50} <200 g/mL, currently category (200-1000 g/mL) and inactive category (>1000 g/mL). Based on the data obtained, only the ethyl acetate extract was classified as a moderate antioxidant, while the other two extracts were inactive. Extracts included in the moderate antioxidant category can still be used as a source of antioxidants [10]. The antioxidant activity was influenced by the flavonoid and phenolic content in the extract. Flavonoids will donate hydrogen atoms or electrons to free radicals to stabilize radical compounds so that the higher the flavonoid content in the extract, the higher the antioxidant activity [35].

Antioxidants play a role in protecting body organs from attack radicals free too. They can stimulate the immune body. Herbal plants like *P.canescens* can be a source of antioxidants because plant materials used contain compound metabolites secondary such as flavonoids, tannins, and phenolic. Radical free on the body causing there is energy in many natural causes happening rheology, such as coagulation blood. Consequently, radical free that is not under control by COVID-19 causes an energy struggle between a host and the human body. Height rate is remarkably free inside the body generated by low activity antioxidants [36].

Antityrosinase

The study by *Maulana. et al.* showed that the n-butanol fraction of *P.canescens leaves* can have qualitative tyrosinase inhibitory activity with a concentration of 5000 ppm, using a solution of the tyrosinase enzyme and L-DOPA observed on TLC plate using UV light, spots that have inhibitory activity tyrosinase will be white. From the results of the study carried out, it was found that the tyrosinase inhibition of the n-butanol fraction of *P.canescens leaves* The appearance of the stain after spraying the tyrosinase and L-DOPA enzyme solution on the appearance of the color with a UV lamp of 254 nm, the appearance of the paint with a UV lamp of 366 nm; Rf value 0.77. L-DOPA is a more competent substrate than L-tyrosine for tyrosinase assay showing clear melanin spots on TLC plates [19].

Immunostimulants

The immune system is the body's defense mechanism against all foreign substances entering the body, including pathogenic microorganisms, consisting of a non-specific and specific immune system [37]. Increased immunity in *M.musculus*, based on the results of a study by *Yani et al*., showed that the extract of the young leaves of *P.canescens* could increase the number of leukocytes. This study was conducted experimentally on *M. musculus* with doses 0.186, 0.375, and 0.5625 mg/kg BW. The results showed that a dose of 0.5625 mg/kg BW could increase the number of leukocytes by 36%. In comparison, given immunes only increased the number of leukocytes by 23%. It was due to some of the active substances contained in the *P.canescens* extract, like peronemin, sitosterol, isopropanol, phytol, diterpenoid, flavonoids, so these elements may help in increasing the number of leukocytes [29].

Rahman et al. showed that *P.canescens* leaf infusion has pharmacological activity as an immunostimulant by increasing leukocytes (white blood cells) carried out in male mice *M.musculus.* The study doses are 5%, 15%, and 20%. Negative control was given 1% Na-CMC. The results of the leukocyte number showed a concentration of 5%, 15%, and 20% higher than the negative control. But, at the 20% concentration leukocyte number above the positive control. The number of leukocytes was significantly different ($p < 0.05$) where 20% more leukocytes were produced than the positive control, based on these results, it was concluded that the infusion of *P.canescens* leaves had an immunomodulatory effect with an increase in the number of leukocytes in mice with a dose of most effective 20%/30 kg BW [38].

One of the ingredients obtained is flavonoids in the phytochemical study of *P.canescens* leaf infusion. Flavonoids are known to have acted as immunostimulants by increasing oxygen and nitrogen radicals, antibody production, cytotoxic activity against tumors by increasing activating receptors and downregulating inhibitory receptors. Therefore, flavonoids are potentially helpful in treating infectious diseases and cancer. Mechanism of action Invitro, flavonoids, and their derivatives inhibit various transcription factors, which modulate the differentiation, proliferation, activation of immune cells and increase the formation of regulatory T cells. Several flavonoids exert anti-inflammatory effects through NF-κB blockade and the NLRP3 inflammasome, inhibiting pro-inflammatory cytokine production, IL-1β, IL-2, IL-6, TNF-, IL-17A, downregulates chemokines, and species reduction[39].

To determine the effect of immunostimulants, the parameter used is the number of leukocytes. This study found that the administration of *P.canescens* leaf infusion can increase the number of leukocytes in mice, where leukocytes are part of the body's immune system. In general, the function of white blood cells is to track and fight microorganisms or foreign molecules that cause disease or infections, such as infections caused by viruses. Leukocytes, namely, neutrophils, monocytes, macrophages, dendritic cells, eosinophils, natural killer cells, innate lymphoid cells, and T cells, become activated in response to viral infection and protect the airway epithelium while triggering the adaptive arm of the immune system [40].

Another study conducted by *Dillasamola et al.* showed that the ethanolic extract of *P.canescens* leaves an immunostimulating effect. This study identified the effectiveness of phagocytosis in killing pathogens using the carbon cleaning method. The parameter used in this study was the number of leukocyte cells in mice. The doses used were, 10, 50, 100, and 200 mg/kg BW, negative control (Na CMC 0.5%). Based on the value of the phagocytosis index, the ethanolic extract of *P.canescens* leaves can affect the percentage of neutrophil cell types in male white mice and significantly affect the increase in the number of leukocytes in male white mice with a dose of *P.canescens* extract at a dose of 200 mg/kg BW showing the highest total leukocyte number [14].

The next study by *Dillasamola et al.* showed that the ethanolic extract of *P.canescens* leaves had an immunostimulating effect by increasing the number of leukocytes in mice using the carbon clearance method leukocytes and the percentage of leukocyte cell types in male mice. In this study, doses of 25, 50, 100 mg/kg BW, Na-CMC 0.5% as a negative control and Stimuno 50 mg/kg BW as a comparison. The extract was given orally once a day for six days with a volume of mice 0.2 ml/20 mg/kg BW immunomodulatory activity study with carbon. Method clearance blood was drawn from the tail capillaries with carbon suspension injected intravenously (iv). The results showed that the ethanol extract of *P.canescens* leaves at doses of 25, 50, 100 mg/kg BW was significantly different from the phagocytosis index value (IF>1), which was studied by the carbon clearance method. Increased total leukocytes could increase the percentage of segmented neutrophil cells against white male mice compared with 0.5% Na-CMC as a control. The results showed an increase in the percentage of segmented neutrophil cell types with increasing doses of the study sample [15].

System immune is system power stand body to attack substance-exposed foreigners to body us. Substance foreign the can be originated from outside nor in body alone. At the same time, substances foreign from the body could be cells dead or changing cells' shape and function—substances foreign the called immunogen or antigens. So, the immune system's role is significant for the body to face various diseases, such as COVID-19, a deadly virus exposed to a low or weak immune system. Because of that, it was important to increase the resistant system body to prevent cases. Many herbal plants can boost the immune system as an immunomodulator. *P.canescens* can increase leukocytes by 36% compared to immune-only 20% [9].

Antidiabetic

Diabetes mellitus (DM) is a chronic metabolic disease caused by insulin deficiency or resistance [41]. A new alternative for antidiabetic has been studied to minimize side effects by utilizing the *P.canescens*, discussed in the following study. Based on a study by *Latief et al.*, ethanol extract of *P.canescens* leaves showed antidiabetic activity by lowering blood glucose levels was quite good in experimental *Mus musculus*, with experimental doses of 175, 350, and 700 mg/kg BW. Alloxan 150 mg/kg BW (negative control) and glibenclamide 3 mg/kg BW (positive control). The antidiabetic activity was carried out based on the previous study by measuring the initial blood sugar levels of mice (H-1) induced, followed by induction of mice with alloxan at a dose of 150 mg/kg BW in all groups. Blood sugar levels were measured in mice, mice with diabetes if (blood sugar levels > 176 mg/dL) to be used in the trial. The study showed that a dose of 350 mg/kg BW provides the most effective activity as an antidiabetic [42].

P.canescens leaf ethanol extract's ability to reduce blood sugar levels in mice was influenced by secondary metabolites such as flavonoids, alkaloids, tannins, saponins, and phenols. Flavonoids and saponins play a role in increasing antioxidant enzymes' activity and regenerating damaged pancreatic cells. Thereby inhibiting insulin deficiency, enzymes that play a role in converting carbohydrates into glucose are glucosidase. Tannins act as astringents that can precipitate intestinal mucous membrane proteins and form a layer that protects the intestinal, thereby inhibiting the absorption of glucose as antidiabetic activity [43].

By inhibiting the glucosidase enzyme, glucose (sugar) levels in the blood will decrease, causing a hypoglycemic effect (reduced blood sugar levels). Flavonoids can lower blood sugar levels by inhibiting GLUT2 of the intestinal mucosa, reducing glucose absorption from the intestinal. Another mechanism by which flavonoids exhibit hypoglycemic effects is by reducing glucose uptake and regulating the activity of enzymes involved in carbohydrate metabolism Diabetes mellitus (DM) is a disease disturbance metabolism that affects insulin action in absorption glucose. People with diabetes are susceptible to infection because of hyperglycemia. Disorders function immunity, vascular complications, and diseases attendant as hypertension, dyslipidemia, and cardiovascular disease. Disease this also becomes a threat to health internationally, which level severity increased in two twenty years last. Severity and mortality from COVID- 19 were higher on a patient with diabetes compared to non-diabetic patients. Suppression of the immunity diabetic patients becomes the factor of the originator accessible to COVID-19 during Pandemic. Therefore, people with diabetes who experience COVID-19 will be more at risk for sharing severe COVID-19, ARDS, up to death [44].

Antipyretic

Antipyretics are a reaction of the body in the form of symptoms that can be caused by infection, pyrogen substrates, proteins, overheating conditions, and immunization. If the temperature reaches 40-41°C, then a critical situation can be fatal because the body can no longer control it [45]. The study by *Putranto & Yani* showed that the extract of *P.canescens* leaves had pharmacological activity as an antipyretic, which was carried out on mice. The study was conducted by inducing DPT-HB fever in *M.musculus* before being treated with extracts at 0.186, 0.375, and 0.5625 mg/kg BW. The results showed that there was no significant difference among each group. However, in decreasing the temperature at P0 = 0.5^oC, P1 = 1^oC, P2 = 0.4^oC, P3 = 1^oC and P4 = 1.1^oC and there is a difference in the temperature drop at P4 is faster, at a dose of 0.5625 mg/kg BW can reduce body temperature 29% better than paracetamol treatment which is only 26% [29] .

Next, *Brata & Wasih* showed that the infusion of *P.canescens* leaves also has antipyretic activity, proven through animal experiments on mice. The study was conducted by induction fever with 5% peptone subcutaneously with a concentration of 10, 20, and 30%, with 5% Na-CMC (negative control) and paracetamol (positive control). Based on the study results, it can be concluded that there was a significant effect. Giving *P.canescens* leaf infusion at a dose of 10% and 20% reduced the body temperature of mice more effectively. *P.canescens* leaf infusion has potential as an antipyretic [46].

Exposure to COVID-19 virus infection causes the sufferer to experience fever. Symptoms other moments suffering from COVID-19: Sick head hurts throat, nausea and vomiting, cough dryness, chest pain, tightness breath. Somebody with a high possibility of antibody fever could be proven damaging for COVID-19 though little opportunity exists. Based on the Case, the body with high fever antibodies can shrink the percentage exposed to COVID-19, the only one using *P.canescens* herbal plant, which has already proven efficacy compound chemical on leaf *P.canescens* character antipyretic [47].

Antihyperuricemia

The potential of *P.canescens* to be developed as an anti hyperuricemia drug will be discussed in the following study. A study conducted by *Latief et al.* showed that the ethanolic extract of *P.canescens* had antihyperuricemic activity with reduced blood uric acid levels that have been carried out in mice (*Mus musculus*) study animals. The study was carried out on mice-induced hyperuricemia by 250 mg/kg BW potassium oxonate intraperitoneally, l-2 mL of chicken liver juice orally. Then, the treatment was discontinued

by giving extract 125, 250, and 500 mg/kg BW and positive control (allopurinol 10 mg/kg BW). Uric acid levels were measured using the Point of Care Study (POCT) method. The study results showed that a dose of 500 mg/kg BW with a percentage of 38.66% gave the best activity in lowering blood uric acid levels in mice [48].

Enzyme uricase can prevent gout from becoming allantoin to increase uric acid levels. Mice in induction with 250 mg/kg BW potassium oxonate acts as an inhibitor of the uricase enzyme. Inhibition of uricase enzyme by potassium oxonate causes uric acid to accumulate and is not eliminated in urine [49]. Alkaloid compounds can inhibit the activity of the XO enzyme, which inhibits uric acid synthesis. In addition, *P.canescens* leaf alkaloid compounds also have anti-inflammatory activity. Colchicine is one of the alkaloid compounds with anti hyperuricemia properties [50].

The World Health Organization (WHO) said: that the elderly occupy the wrong one order top risk group tall contracted COVID-19 after officer health and people with disease attendant as sour veins. That thing is caused because the elderly own low predisposed immunity, so it easily triggers viruses to enter the body elderly. According to the data presented on page official handling of COVID-19 in Indonesia, the group dominating age number death, the result of COVID-19 is elderly 60 years old to one with 42.3%. Avoiding it from the sour disease tendon is a strong possibility of low to risk exposure to COVID-19 because the immune body is still good [51].

Anti-inflammatory

Inflammation is the body's response to injury or tissue damage to protect the body, which aims to destroy or reduce the injured agent/tissue [52]. *P.canescens* plant was suspected of having anti-inflammatory activity, and this can be strengthened in the discussion of the subsequent Study trials. The Study by *Latief et al* . showed that the ethanolic extract of *P.canescens leaves* had an anti-inflammatory activity of up to 50% in mice (Mus musculus). The study was carried out using a combination of two study methods, namely the granuloma sac formation method and the edema manufacturing method on the back of mice, which had previously been induced by 2% carrageenan subcutaneously. The concentrations of ethanol extract used for treatment were 5, 10, and 15%. The results showed that the section of *P.canescens* leaf ethanol affects the average volume of exudate and percentage inhibition of inflammation. The extract concentration of 15% was able to reduce the volume of exudate by 46.67±5.5061 and the inhibition of inflammation by 87.78%. The study results showed that 15% of *P.canescens* leaf ethanol extract had anti-inflammatory activity, reaching 50% inhibition [17].

The decrease in the average number of neutrophils can be caused by bioactive compounds of the flavonoid group in the ethanolic extract of the leaves *P. canescens*. The ethanol extract is a crude extract, so the combination cannot determine specific metabolites that provide anti-inflammatory effects. Flavonoid compounds play a role in inhibiting arachidonic acid cyclooxygenase and lipoxygenase, thus inhibiting the synthesis of prostaglandins and leukotrienes indirect reduction of inflammatory mediators direct inhibition of leukocyte accumulation in the area of inflammation. Under normal conditions, leukocytes move freely along the endothelial wall, but mediators cause leukocyte adhesion to the endothelial barrier and cause immobile leukocytes [53].

The decrease in the volume of exudate can be caused by the content of active compounds in the exudate *P.canescens* leaves, one of which is a flavonoid that can play a role by binding to the side active on the COX-1 enzyme so that it can interfere with the transcription process so that it can interfere with COX-2 expression through inhibition of transactivator binding. NF. kB and blocking the entry of coactivators that function as COX-2 promoters. The COX-1 enzyme synthesizes prostaglandins; if there is a disturbance in the transcription and expression of COX-2, their production will be reduced. In addition, flavonoids can prevent the production of Inducible Nitric Oxide Synthase (iNOS). When inflammation occurs, pro-inflammatory cytokine products induce iNOS and produce large amounts of iNOS. iNOS has an effect as a vasodilator so that when the process is inhibited, edema will decrease [54].

Sufferers of severe COVID-19 infection experience symptom fever, quickly tired, sick head, painful muscles, cough, and crowded breath on condition that inflammatory process occurs on channel breathing; however, inflammation excessive could result in death. Inflammation is an effective mechanism for protecting oneself from things foreign with release substances such as histamine, prostaglandins, serotonin, C-Reactive Protein (CRP), and fibrinogen which will cause a reaction from the body with formation inflammation. With the blocked release from substances, the use of compound chemical metabolites existing secondary on *P.canescens* so risk happening inflammation consequence small COVID-19 exposure occur even can be stopped [54].

IV. CONCLUSION

Based on various studies that have been studied and reviewed, it can be concluded that the sungkai *(P. canescens)* has many health benefits, ranging from mild to severe illnesses. Phytochemical screening based on literature review articles with specific chemical reagent study, *P.canescens* contains secondary metabolites, like alkaloids, flavonoids, terpenoids, steroids, saponins, phenolics, and tannins. The pharmacological activity of

P.canescens was anticancer, antimicrobial, antimalarial, antioxidant, anti-tyrosinase, immunostimulant, antidiabetic, antipyretic, antihyperuricemic, and anti-inflammatory.

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