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Review Article

A REVIEW OF SUNGKAI (*PERONEMA CANESCENS*): TRADITIONAL USAGE, PHYTOCONSTITUENT, AND PHARMACOLOGICAL ACTIVITIES

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ABSTRACT

This article review aims to evaluate the traditional usage, phytoconstituent, and pharmacological activities of *Peronema canescens* (PC) published between 1994 to 2021 and suggest directions for further in-depth research of PC as a medicinal resource. A literature review used relevant keywords to collect primary and secondary scientific papers from popular media databases such as Google Scholar, Scopus, PubMed, and Science Direct. The search keywords for papers included *Peronema canescens*, traditional usage, phytoconstituent, pharmacological activity, *in vitro*, *in vivo*, combined, or separated. Traditional usage of PC as medicine has been identified to treat various diseases such as toothache, malaria, fever, skin disorders, itching, bruising, and hypertension, as refreshing drinks, increasing stamina, and as food ingredients. Chemical constituents of PC were seven clerodane diterpenoid compounds, namely A2, A3, B1, B2, B3, C1, and D1 peronemin. Five of them are furanyl groups. Secondary metabolites contained in PC extract were phenols, triterpenoids, flavonoids, tannins, alkaloids, steroids, and saponins. *In vitro*, pharmacological activities of PC showed anti-plasmodium, anti-inflammatory, antioxidant, antidiabetic, cytotoxic, and antibacterial activities, had non-toxic effects, and did not cause teratogenic effects. *In vivo* studies of PC showed that PC could use as an immune booster, antiparasitic, anti-hyperuricemic, anti-plasmodium, antidiabetic, and antipyretic. Many phytoconstituent and pharmacological reports indicated that PC was an essential medicinal herb resource, and some of its traditional uses, including the treatment of fever, antiparasitic, anti-hypertension, malaria, and tonic drink, have been partially confirmed through modern pharmacological studies. Diterpenoids were the main active constituents. However, these crude extracts and isolated chemicals of PC required additional research to identify the effects, optimal dosage, mechanisms of action, long-term safety, and potential side effects. In addition, clinical research was necessary to support the therapeutic potential of PC.

Keywords: Sungkai, *Peronema canescens*, Traditional usage, Phytoconstituent, Pharmacological activities, *In vitro*, *In vivo*

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INTRODUCTION

Herbal remedies have been used worldwide for centuries to cure and prevent various diseases, especially in developing nations where infectious diseases are prevalent [1]. Data from WHO 2018, stated that 170 WHO members recognize the use of traditional and complementary medicines (TandCM), 50% of 194 WHO member states have national policies on TandCM, and 127 WHO member states report the existence of laws regulating herbal medicines [2]. The interest in natural products has produced several remarkable outcomes, and pharma corporations accepted natural products as modern and effective tools for new pharmaceuticals and drug leads [1]. However, much data on traditional medicines has not been reported, especially from Indonesia. One of the critical efforts to address these challenges is utilizing traditional and complementary medicinal resources [3].

Peronema canescens (PC) is a medicinal plant from the *Verbenaceae* family. In Indonesia, PC is known as *Sungkai* [4]. PC is a native Indonesian plant located in the West Sumatera, Riau, Jambi, Bengkulu, Lampung and South Sumatera (in Sumatera island), West Kalimantan, Central Kalimantan, East Kalimantan and South Kalimantan [5]. PC is a shrub or small to medium-sized tree that can grow 20-30 m tall, and the bole is straight or slightly flexible, limbless for up to 9 to 15 m, up to 70 cm in diameter, and typically with tiny buttresses. The root system is shallow and has a short taproot. The bark's surface is fissured, fibrous, scaly, and dirty grey or light buff. The crown is ovoid, has four-angle twigs, and is densely short-haired [6].

Ethnobotanical studies related to PC showed that the plant parts used were leaves and stems [7-9]. Traditionally, PC leaves are mainly used for immune boosting. Decoctions are taken orally for immune boosting [5, 6]. PC's stem was used as a medicine and a tonic drink on Kalimantan island, Indonesia [10]. In other studies, PC was also used for malaria [11]. Phytochemical constituent studies showed seven clerodane diterpenoids isolated from PC, namely Peronemin A2, A3, B1, B2, B3, C1, and D1 [4, 12]. PC has also been reported to contain numerous secondary metabolites such as phenols, tannins, alkaloids, steroids [13], flavonoids, saponins [14], and triterpenoids [15], which display various biological effects such as antioxidants [5], Immune-boosting and anti-inflammatory [16].

This article is the first to evaluate the PC. Other than this article, no review articles on PC have been published. This review aimed to conduct scientific studies on articles that reported 1994-2021 to describe PC's traditional usage, phytoconstituent, and pharmacological activities. The performed bioactivity test could serve as the basis for treatment.

MATERIALS AND METHODS

The method used to review articles was a literature study, by collecting primary or secondary scientific articles from databases such as PubMed, Scopus, Science Direct, and Google Scholar by using various relevant keywords such as "*Peronema canescens*", "traditional usage", "phytoconstituent", "pharmacological activity", "*in vitro*", "*in vivo*", either combined or separated." The relevant articles were selected from 2021 and below from the articles collected. The duplicated papers must be manually deleted. All articles were initially examined based on their title, abstract, and methodologies to be designated before the final valuation. Then, the appraisal was based on criteria for inclusion and exclusion. The inclusion criteria in this article are (1) PC traditional usage and

phytoconstituent, (2) activity test by *in vitro* and *in vivo*, (3) published between 2021 and below, (4) articles collected in English and Bahasa that had abstracts in English, and (5) including any research designs, while the exclusion criteria in this article are articles in the topic of a review paper. A total of 41 publications were chosen for a more in-depth examination.

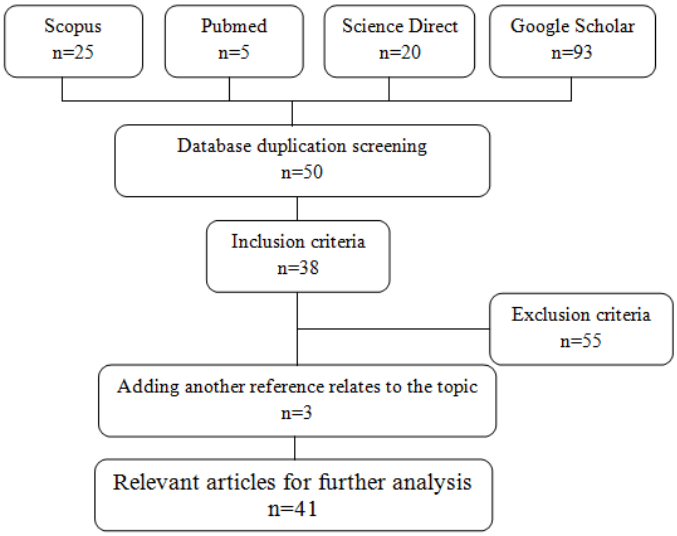


Fig. 1: Flow diagram showing an article review methods

RESULTS

Table 1: Reported traditional uses of *Peronema canescens*

Plant parts	Traditional use	Preparation	Ethnic group	Reference
Leaves	Antiparasitic	Leaves rubbed on the body when taking a bath as anti-scabies	Seberida, Riau Province, Indonesia	[17]
Leaves	Increase stamina	Boil in water and drink once every day before breakfast	Baduy people, Java Island, Indonesia	[8]
Leaves	To cure high blood pressure	Not explained	Dayak Ot Danum, Central Kalimantan, Indonesia	[18]
Leaves	Toothache, fever, dermatosis, and malaria	Not explained	Central Kalimantan, Indonesia	[19]
Leaves	Health supplements, Traditional medicine	Boil in water and drink. The time to drink is not explained	Dayak, Central Kalimantan, Indonesia	[7]
Leaves	Postpartum recovery	Not explained	Bukit Rimbang, Riau, Indonesia	[20]
Leaves	Malaria	Not explained	Central Kalimantan, Indonesia	[11]
Leaves	Treats itching, bruising, malaria	Not explained	Rejang Ethnic, Bengkulu, Indonesia	[21]
Leaves and Tree	Traditional postpartum bath (mandi serom)	Leaves mixed with water for bathing	Kedah, Malaysia	[22]
Wood, bark, leaves	Stomach pain, wounds, white skin blotches	Not explained	Dayak people, East Kalimantan, Indonesia	[23]
Barks	Malaria and tonic drink	Boil in water and drink once every day before breakfast	Balikpapan, East Kalimantan, Indonesia	[10, 24]
Young leaves	Fever	Not explained	Dayak Tunjung, East Kalimantan, Indonesia	[25]
Root	Diuretic and pains	Not explained	Dayak Tunjung, East Kalimantan, Indonesia	[25]

Table 2: Phytoconstituents from *Peronema canescens*

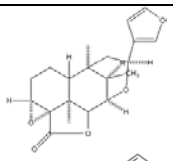
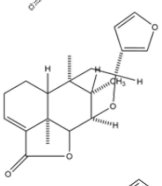
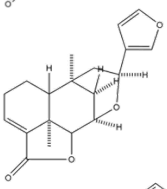
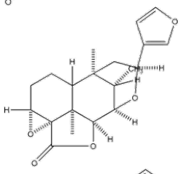
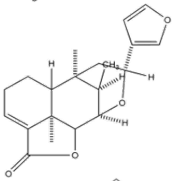
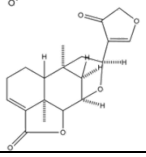
Plant parts	Sample	Phytoconstituents	References
Leaves	Isolate	Clerodane-type diterpenoids	[12]
		Peronemins B1, B2, A2, A3, B3, C1, D1, actenoides, isomer actenoides, and flavonoid glycosides	[26]
Leaves	Chloroform	Peronemins, catechol, quinine acid, isovanillin acid and guaiacol (Clerodane-type diterpenoids)	[27]
Leaves	Extract ethanol	Phenol, flavonoids, tannins, alkaloids, steroids, saponins	[13]
Leaves	Dry PC	Flavonoid, saponin, tannin	[14]
Leaves	Crude extract ethanol	Triterpenoids, phenolics, alkaloids, saponins, flavonoids, and steroids	[15]
Leaves	*n*-hexane	Triterpenoids, steroids, and flavonoids	[15]
Leaves	Ethyl acetate	Triterpenoids, steroids, and alkaloids	[15]
Leaves	Residual ethanol	Alkaloids, flavonoids, phenolics, and steroids	[15]

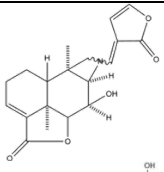
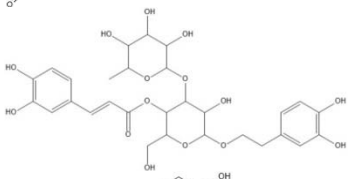
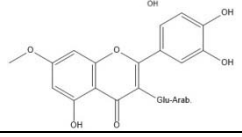
Table 3: Pharmacological activity of *Peronema canescens*

Plant parts	Activity studies	Study	Method	Extracts/ active constituent	Observed effect	Reference
Wood	Tyrosinase activity	*In vitro*	Tyrosinase activity	Methanol	Relative activity 106 %	[28]
Leaves	Glucosyltransferase inhibitory activity	*In vitro*	glucosyltransferase (GTase) inhibitory	50% aqueous ethanol extracts	Percent Inhibition 6.7 %	[29]
Leaves	Anti-plasmodium	*In vitro*	Haem Polymerization inhibition activity	Acetone, ethanol, aqueous	IC_{50} acetone 0.40±0.17 mg/ml, ethanol 1.46±0.05 aqueous 53.89±39.47 mg/ml	[30]
Leaves	Anti-inflammatory	*In vitro*	Lipoxygenase Inhibitory	Methanol extract	IC_{50} 25.64 µg/ml	[31]
Stem	Anti-inflammatory	*In vitro*	Lipoxygenase Inhibitory	Methanol extract	IC_{50} 33.65 µg/ml	[31]
Leaves	Photo-cytotoxic	*In vitro*	photo-cytotoxic activity using a cell viability test using a human leukemia cell line HL60 for photodynamic therapy	Methanol	20 µg/ml were tested against 15,000 HL60 cells that have photo-cytotoxic activity	[32]
Leaves	Antibacterial	*In vitro*	Minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC)	Methanol	(MIC) 20% for bacteria *S. mutans*, S. *Typhi*, and S. *aureus*. 15% for bacteria *B. subtilis*. (MBC) 5% for *S. mutans* and *S. Typhi*. 1 % *B. subtilis* and *Staphylococcus aureus*	[33]
Leaves	Antidiabetic	*In vitro*	antidiabetic properties model 3T3-L1 adipocytes model 3T3-L1 adipocytes	Distilled water	Adipogenesis (↓), Adipolysis (↑), Glucose uptake (↑), Glucose Consumption (↓)	[34]
Leaves	Cytotoxic	*In vitro*	Brine shrimp lethality test (BSLT)	Methanol an dn-hexane fraction	LC_{50} methanol 387.257 ppm, n-hexane 107.399 ppm	[35]
Leaves	Teratogen	*In vitro*	effects on the development and growth of the feta external of *Mus musculus*	Ethanol	Dose of 0.75 mg/kg	[36]
Leaves	Anti-plasmodium	*In vitro*	Strains of Plasmodium falciparum D10 and FCR3	Acetone, ethanol, and aqueous extracts	Acetone (26.33±1.65), ethanol (37.96±8.17), and aqueous (12.26±1.05) µg/ml against Plasmodium falciparum D10 strain and acetone (51.14±8.65), ethanol (70.22±14.13) and aqueous (34.85±6.04) µg/ml, against FCR3 strain	[37]
Leaves	Cytotoxic	*In vitro*	Vero cells using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT)	Acetone, ethanol, and aqueous extracts	IC_{50} Acetone (23.37±5.63), ethanol (629.46±24.85), and aqueous (634.00±144.82)	[37]
Leaves	Antioxidant	*In vitro*	DPPH, TEAC, and FRAP	Methanol extract	IC_{50}±SD (µg/ml) DPPH 9.389±0.679; TEAC 120.28±0.12; FRAP 266.33±20.87	[38]
Leaves	Antibacterial	*In vitro*	Kirby-Bauer's disc method	Ethanol	A concentration of 25% inhibits the growth of *Escherichia coli* at 3.75 mm	[39]
Leaves	Anticancer (Cytotoxic activity)	*In vitro*	Colon cancer HT-29 cells	Chloroform fraction and subfraction	IC_{50} 14.807 to 34.448 µg/m	[40]
Leaves	Antioxidant	*In vitro*	2,2′-diphenyl-2-picrylhydrazyl (DPPH)	Ethanol extract, N hexane fraction, ethyl acetate fraction, residual ethanol	Ethanol Extract IC_{50} 29.549 µg/ml: N Hexane Fraction IC_{50} 607.475 µg/ml; ethyl acetate fraction IC_{50} 12.986 µg/ml; residual ethanol IC_{50} 15.766 µg/ml	[15]
Leaves	Antioxidant	*In vitro*	Qualitative with TLC	Butanol extract	Yellow spot after spraying with DPPH reagent	[41]
Leaves	Anti-tyrosinase	*In vitro*	Qualitative with TLC	Butanol extract	White spot after spraying with tyrosinase and L-DOPA	[41]
Leaves	Immunomodulatory	*In vitro*	LPS stimulated RAW 264.7 cells to produce TNF and IL-6.	Ethanol extract	Dose of 100 µg/ml for TNF-α 608.66±34.85 and IL-6 4.95±0.15	[42]
Leaves	Antiparasitic	*In vivo*	Antiparasitic activity	Ethanol	At an intraperitoneal B. gibsoni dose of 0.7 g/kg body weight, the IC_{50} (g/ml) was 43.8 3.5 without acute toxicity in mice.	[43,44]
Leaves	Toxicity	*In vivo*	Percent of death	Ethanol	Extract ethanol at a dose of 0.7 g/kg of body weight, and there will be no fatalities.	[43]
Leaves	Antipyretic	*In vivo*	DPT-HB fever	Ethanol	The dose of 0.5625 mg/kg 37.4 reduce to 36.5 °C	[45]

Plant parts	Activity studies	Study	Method	Extracts/ active constituent	Observed effect	Reference
Leaves	Immunomodulatory	*In vivo*	number of leukocytes	Ethanol	Dose of 0.5625 mg/kg increase leukocytes by 36%	[45]
Leaves	Anti-inflammatory	*In vivo*	Carrageenan Induced	Isolate	Isolate of 15 percent. It had the most excellent inflammation inhibition of 60.88%.	[46]
Leaves	Anti-inflammatory activity	*In vivo*	Carrageenan Induced	Ethanol	Extract ethanol concentration of 15% reduced exudate volume by 46.67±5.506 µl and reduced inflammation by 87.78%.	[47]
Leaves	Immunomodulatory	*In vivo*	Carbon Clearance Method	Ethanol extract	Dose of 100 mg/kg phagocytic index 1.548 and total leukocytes 12 558±2536	[48]
Leaves	Immunomodulatory	*In vivo*	percentage of phagocytic and leukocytes, injection of a *Staphylococcus aureus*	Ethanol extract	Dose of 800 mg/kg BW for phagocytic capacity 309.17±7.88 and total leukocytes. 12 516±952.72	[42]
Leaves	Antidiabetic	*In vivo*	Mice Induced alloxan 150 mg/kg. The Easy Touch GCU is used for Point-of-Care (POCT) testing.	Ethanol extract	Dose of 350 mg/kg BW Reduces blood glucose levels, urine output, daily fluid intake, and body mass.	[13]
Leaves	Antihyperuricemia	*In vivo*	hyperuricemia, induced by 250 mg/kg B.W. potassium oxonate (i. p) and 2 ml/200 g BW of chicken liver juice orally for six days	Ethanol extract	A 500 mg/kg BW dose decreases uric acid levels to 38.66%.	[49]
Leaves	Immunomodulatory	*In vivo*	Carbon Clearance Method	Ethanol extract	Dose of 200 mg/kg total leukocytes 15 910	[50]

Table 3: Phytocostituent chemical structure of *Peronema canescens* [26, 27]

No	Compounds	2D Chemical structure
1	Peronemin A2	
2	Peronemin A3	
3	Peronemin B1	
4	Peronemin B2	
5	Peronemin B3	
6	Peronemin C1	

No	Compounds	2D Chemical structure
7	Peronemin D1	
8	Acteoside	
9	Flavonoid glycosides	

DISCUSSION

Traditional medical uses

Traditional medicine refers to health practices, techniques, knowledge, and beliefs that integrate plants administered singularly or in combination to cure, diagnose and prevent illnesses from obtaining a healthy life [51]. The traditional usage of PC, as described in this article, involves boiling fresh leaves and drinking them in a specified dose [7] as well as rubbing leaves on the body during a bath [22]. Traditional PC is used for hard work, anti-scabies, malaria, tonic drinks, health supplements, postpartum recovery, toothache, fever, dermatosis, treating itching, bruising, hypertension, stomach pain, sores, white patches on the skin, hepatitis, diuretics, and pain. The plant uses leaves, stems, wood, bark, and root. The dosage used is not described based on literature obtained for traditional use. However, traditional uses and how to use PC are summarized in table 1.

Phytoconstituent studies

Medicinal plants have at least one of their components (leaves, stems, bark, and roots) used for medicinal purposes. Seven clerodane diterpenoid compounds of PC were isolated, namely A2, A3, B1, B2, B3, C1, and D1 peronemins [4, 12]. In other studies, PC contained acteoside and flavonoid glycosides [26]. According to [27], the best mobile phase of thin-layer chromatography (TLC) used for the phytochemical analysis of PC was hexane: ethyl acetate: isopropanol (7:3:0.3). In a study (Hazimi *et al.*, 2018) PC containing phytochemical compounds such as flavonoid, saponins, and tannins. The phytochemical structure contained in PC is shown in table 2 and table 3.

Pharmacological activities

Twenty-six articles discussed pharmacological activity, 19 articles discussed *in vitro*, 12 articles discussed *In vivo*, and several discussed both. The reviewed pharmacological activities were anti-hyperuricemia, anti-plasmodium, antibacterial, anticancer (cytotoxic activity), antidiabetic, anti-inflammatory, antioxidant, antiparasitic, antipyretic, anti-tyrosinase, glucosyltransferase inhibitory activity immunomodulatory, photo-cytotoxic, teratogen and tyrosinase activity. The pharmacological activities of *In vitro* and *In vivo* studies in PC are shown in table 3.

In vitro studies

Anti-plasmodium

The use of PC as anti-plasmodium had been reported by [37] that IC_{50} values for acetone, and water extracts against *Plasmodium falciparum*, strains D10 were 26.33±1.65; 37.96±8.17; and 12.26±1.05 g/ml, respectively. Against strain FCR35, 1.14±8.65; 70.22±14.13; and 34.85±6.04 g/ml, respectively. The same article added that aqueous extract of PC leaves showed great anti-plasmodial activity *In vitro* related to efficacy and the high selectivity index. Method using *Plasmodium falciparum* strains D10 and FCR3, Human erythrocytes (O blood type) with 1% hematocrit were cultured in RPMI 1640 (Sigma) with 25 mmol HEPES (Sigma) and 30 mmol $NaHCO_3$. The parasite cultures were grown in a petri dish at 37 °C with gentamicin (25 mg/l) and human serum (O blood type) at 10%. Every day, the media was observed. The parasite cultures were synchronized using 5% sorbitol.

According to [30], Haem polymerization inhibitory activity with IC_{50} of acetone extract was 0.40±0.17 mg/ml, ethanol extract was 1.46±0.05, and water extract was 53.89±39.47 mg/ml, PC acetone extract had the highest haem polymerization inhibition activity. Eppendorf tubes were filled with 100 ml of a 1 mmol hematin solution in 0.2 M NaOH, and then 50 ml samples of different dose levels were added. Aqueous was used as a control. The Eppendorf tube was filled with 50 ml of glacial acetic acid solution (pH 2.6) and then incubated at 37 °C for 24 h. A solution in the Eppendorf tube was centrifuged and washed with DMSO 200 µl. The precipitate was treated with 200 ml NaOH 0.1 M. Every 100 ml was placed in 96 microplates, IC_{50} value was analyzed using an ELISA reader at a wavelength of 405 nm.

Cytotoxic activity

On Vero cells, PC was performed in a 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide cytotoxic assay. IC_{50} values for acetone, ethanol, and water extracts were respectively 37±5.63; 629.46±24.85; and 634.00±144.82 g/ml [37], a method used for one µL volume containing one× 10 ^{4}A 96-well plate was filled with Vero cells in culture medium and incubated for 24 h at 37 °C and 5% CO_2. Next, 100 µl leaves extract of different concentrations in a culture medium was added and cultivated for 72 h at 37 °C, with 5% CO_2. After collecting the culture material using a micropipette, 100 µl was added with 10 µl MTT solution, then incubated at 37 °C and 5% CO_2 for 4 h. Finally, a 100 µl solution of 10% SDS in 0.01 M HCl was added to dilute the formazan. Furthermore, the sample was incubated at room temperature for 18 h. The sample was analyzed using an ELISA reader at a wavelength of 595 nm, and absorbance was determined. The IC_{50} values were calculated.

According to [35], PC leaves extract was tested using the brine shrimp lethality test (BSLT) against *Artemia salina* Leach larvae. The value of LC_{50} of methanol extract was 387.257 g/ml, and n-hexane was 107.399 g/ml. Based on the BSLT method, a section said active if the LC_{50} value was<1000 g/ml. The smaller the 1000 g/ml LC_{50} value, the more cytotoxic the extract. The test was conducted using ten larvae aged 48 h in a vial containing the ethanol extract solution and the n-hexane fraction solution of PC leaves. Each treatment group was replicated five times. The final volume of each vial was 5 ml. The vial was placed under lighting for 24 h, and the number of dead larvae was counted.

Anticancer activity

Chloroform fraction and subfraction of PC leaves could be examined for their cytotoxicity (IC_{50}) on HT-29 colon cancer cells using *In vitro*

cell lines test. 4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assays with concentrations of 1.563 to 200.00 µg/ml were used to examine the cytotoxic effects of a substance on HT-29 cells. Alkaloids, terpenoids, steroids, flavonoids, and phenolics were the secondary metabolites discovered in the chloroform fraction. The cytotoxic (IC_{50}) value against HT-29 colon cancer cells varied between 14.807 µg/ml and 34.448 µg/ml [40].

Anti-inflammatory

The IC_{50} value of PC leaves methanol extract was 25.64 g/ml, and the IC_{50} of PV stems extract was 33.65 g/ml through the Lipoxygenase inhibition mechanism [31]. The method used enzyme activity in borate buffer (0.2 M, pH 9.0) was measured spectrophotometrically by the increase in absorbance at 234 nm, 25 °C between 50 to 210 s after the administration of lipoxygenase (167 U/ml. final concentration), using linoleic acid as substrate (134 µM). The enzyme solution was kept on ice before the test samples, and controls (100 percent enzyme activity) were evaluated. Enzyme inhibitory activities were calculated by measuring the increase in absorbance per unit of time with a spectrophotometer. The enzyme solution was preincubated with the test sample for 5 min at 25 °C, followed by the substrate solution and borate buffer to a final volume of 3.0 ml. The enzyme activity was measured as the absorbance change rate per unit. A dimethylsulfoxide (DMSO) solution containing fisetin was added as a positive control. The enzyme inhibitory activity was reported as the ratio of the difference in enzyme activity between the test sample and the control compared to the enzyme activity in the control experiment.

Antidiabetic

Cell viability was used to determine antidiabetic activity using the 3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide (MTT) assay. For further analysis, the crude extracts were weighed and frozen at-80 °C. 3T3-L1 preadipocytes were grown in Dulbecco's Medium Eagle Medium (DMEM) with 10% fetal bovine serum (FBS), 1% penicillin (10 000 U/ml), and 1% streptomycin (10 g/ml) was added. After the cells were confluent, it was cultured every 2-3 d. From the cultured cells, the supernatant was taken, thrown away, and washed twice with phosphate-buffered saline A (PBSA). This method was used to eliminate serum residues inhibiting trypsin's function. PC aqueous extract showed *In vitro* antidiabetic activity with the 3T3-L1 adipocyte model. These findings showed that there was an effect on adipogenesis (↓), adipolysis (↑), glucose uptake (↑), and glucose consumption (↓) [34].

Antioxidant

Antioxidant activity test using DPPH (1,1-diphenyl-2-picrylhydrazyl) method IC_{50} value obtained of PC in ethanol extract was 29.549 g/ml: n-hexane fraction was 607.475 g/ml; ethyl acetate fraction was 12.986 g/ml; residual ethanol was 15.766 g/ml. Based on GC-MS characterization, several compounds were identified, such as alkanes, alkenes, alcohols, and fatty acids [15]. According to [38], PC leaves methanol extract had an IC_{50} value of (µg/ml), antioxidant against DPPH value was 9.389±0.679, Trolox equivalent antioxidant capacity (TEAC) was 120.28±0.12 and ferric reducing antioxidant power (FRAP) was 266.33±20.87. According to [41], a yellow-white spot was formed after spraying with DPPH reagent using thin-layer chromatography.

Antibacterial

The Minimum Inhibition Concentration (MIC) value of PC methanol extract against *Streptococcus mutans, Salmonella typhi, and Staphylococcus aureus* was 20%, while *Bacillus subtilis* was 15%. The Minimum Bactericidal Concentration (MBC) value of PC methanol extract at a concentration of 5% was practical as bactericidal against *Streptococcus mutants* and *Salmonella typhi*. In comparison, a concentration of 1% was effective as a bactericidal against *Bacillus subtilis* and *Staphylococcus aureus* [33]. According to other research [39], PC leaves ethanol extract had antibacterial activity against *Escherichia coli,* using the Kirby-Bauer disc method at concentrations of 25%, 50%, 75%, and 100%, as shown by the presence of inhibition zones measured were 3.75 mm, 3.5 mm, 3.5 mm, and 7.75 mm, respectively. Consecutively, with an adequate concentration of 25%.

Teratogenic

According to [36], their research proved that the administration of PC leaf extract up to 0.75 mg/kg BW to *Mus musculus* as an animal test on the parameter period of organogenesis resulted in no statistically significant effect on how the fetus of animal test grew or changed on the outside. This study found that PC leaves extract usage at a maximum dose of 0.75 mg/kg BW was safe.

Glucosyltransferase inhibitory activity

50% aqueous ethanol extract of PC could inhibit glucosyltransferase activity with 6.7% Inhibition. *Streptococcus sobrinus* (*S. sobrinus*) was cultivated on Todd-Hewitt (T. H.) broth agar at 37 °C for 24 h. *S. sobrinus* was placed in 40 ml of T. H. broth, and after 24 h of incubation at 37 °C, it was transferred to 4 L of T. H. broth. After incubating at 37 °C for 20 h, it was centrifuged (1300 g) at 4 °C for 10 min. The broth's precipitates were taken out with 8 M urea solutions for one hour and then dialyzed against a 10 mmol sodium phosphate buffer (pH 6.0). The substrate solution contained 0.5% sucrose, sample solution, and a predetermined amount of crude GTase solution was incubated at 37 °C for 3 h. The absorbance value of the solution was measured turbidimetrically at a wavelength of 550 nm.

Tyrosinase inhibitory activity

Methanol extract of PC could inhibit tyrosinase activity with relative activity of 106 % [28]. Therefore, samples were dissolved in 2.5 mmol DMSO as much as 333 µl. Next, the solution of l-DOPA or l-tyrosine was mixed with 600 µl of 0.1M phosphate (pH 6.5) and then incubated at 25 °C. Then, 33 µl of the sample and 33 µl of the aqueous solution of mushroom tyrosinase (1380 units/ml) were added, and the initial linear increase in optical density was measured at a wavelength of 470 nm. Based on the synthesis of dopachrome, it was recorded immediately.

Immunomodulatory

According to [42], LPS-induced TNF-α and IL-6 production in RAW 264.7 macrophage cells. A dose of 100µg/ml had activity as immunomodulatory for TNF-α of 608.66±34.85 and IL-6 of 4.95±0.15. The method used was a 24-well plate containing the previous cell suspension in each test well. In addition, 100 µl of the prepared test solution was added. The standard control well contained 900 µl of cell suspension, whereas the blank well contained 900 µl of media. The plates were incubated again for 2 h. After 2 h, pour the LPS solution into each well until a concentration of 1 µg/ml is reached, and then incubated for 24 h. After that, the medium was centrifuged for 20 min at 2000 RPM and 2-8 °C. An ELISA reader was used to measure the levels of TNF-α and IL-6 in the supernatant.

Photo-cytotoxic

The photo-cytotoxic activity was tested using a cell viability test against human leukemia cell line HL60 for photodynamic therapy. 15 000 HL60 cells were tested at 20 µg/ml, with photo-cytotoxic activity. Using the MTT test, sample solution in DMSO with a concentration of 20 mg/ml as a stock solution, then diluted appropriately in phenol red-free culture medium added with 5% FBS. The concentration of extract 20 µg/ml was tested against 15 000 HL60 cells per well in a 96-well plate at 37 °C and 5% CO_2 for 2 h. There were four replica wells for each test substance [32]. The results prove that the PC leaves extract had photo-cytotoxic. However, the PC stem extract did not have photo-cytotoxic activity.

Antiparasitic

IC_{50} (µg/ml 43.8±3.5) value for PC leaves ethanol extracts as antiparasitic activity against *Babesia gibsoni* [43]. The method used to evaluate antiparasitic activity, namely sample was mixed with dimethyl sulfoxide (DMSO) and diluted in RPMI 1640 medium with sodium pyruvate (0.1 mg/ml), glutamine (0.3 mg/ml), sodium bicarbonate (2 mg/ml), penicillin (100 units/ml), and streptomycin (100 µg/ml). The final DMSO concentration was less than 0.1%. Erythrocytes were resuspended to a final packed cell volume of 6% in a culture medium of 60% RPMI 1640 and 40% average serum,

then washed. At the start of incubation, the erythrocyte suspension was mixed with parasitized erythrocytes to achieve 0.5–1.0 % parasitemia. The experiment was conducted in a 96-well culture plate, with 25 µl of parasitized erythrocyte suspension and 25 µl of extract solution containing the appropriate amounts of each extract in each well. The solution that contained extracts had final concentrations of 0; 1.9; 3.9; 7.8; 15.6; 31.2; 62.5; 125; 250; 500; and 1000 µg/ml. The plate was incubated at 37 °C in a humidified atmosphere that contained 5% CO_2, 5% O_2, and 90% N_2. After incubating the plate for 72 h, a thin, smeared, Giemsa-stained sample was taken. The number of parasitized cells was counted to fig. out the parasitemia level.

***In vivo* studies**

Immunomodulatory

According to [45], the most effective dose in increasing the immune system with PC ethanol extract was 0.567 mg/kg BW. Increases the number of leukocytes by 36%, better than the comparison dose (immunos®), only increases the number of leukocytes by 23% against diphtheria, pertussis, tetanus-hepatitis B (DPT-HB) fever-induced. On the other hand, an Immunomodulatory activity test was conducted using a percentage of phagocytic and leukocytes, with *Staphylococcus aureus* induced. The dose of 800 mg/kg BW for phagocytic capacity value was 309.17±7.88, and the dose of 800 mg/kg BW for total leukocytes value was 12516±952.72/µl of blood. According to [48], with the carbon clearance technique, a dose of 100 mg/kg phagocytic index was 1.548, and total leukocytes were 12558±2536.

Anti-hyperuricemia

The treatment group of PC leaves ethanol extract at a dose of 125-500 mg/kg BW could reduce uric acid levels in mice, and a dose of 500 mg/kg BW with a 38.66% decrease was the optimal dose for reducing uric acid levels in mice [49]. The mice were used for hyperuricemia with an administered dose of potassium oxonate was 250 mg/kg BW intraperitoneally and 2 ml/200 BW. of chicken liver juice for six days. On day 7th, the mice's blood was taken to analyze the increased uric acid level after induction. Mice had hyperuricemia when their uric acid levels were 1.7-3.0 mg/dl, while normal uric acid levels in mice were 0.5-1.4 mg/dl.

Anti plasmodium

PC ethyl acetate fraction dose of 0.056 g/kg BW could inhibit the growth of parasitemia in 50.89%, where the percentage of inhibition was more significant than in the positive-negative control groups. The parasitemia development rate was calculated by observing the *Mus musculus* blood smear stained with Giemsa under a microscope. Parasitemia, parasite growth rate, and parasitemia inhibition in the blood determined the anti-plasmodium activity test [52].

Antidiabetic

The ethanol extract of PC leaves could reduce blood glucose levels in mice. The ethanol extract of PC leaves at a dose of 350 mg/kg BW has the most potential to reduce blood glucose levels and urine volume. The urine volume of mice was directly proportional to their daily water intake and blood sugar levels. Therefore, a higher blood sugar level will cause the body to excrete sugar through the urine, increasing urine volume (polyuria) [13]. Alloxan induction was used at 150 mg/kg BW for all groups.

Antipyretic

0.5625 mg/kg BW of PC leaves ethanol extract could reduce the body temperature by 29%, better than the paracetamol treatment, which could only reduce the body temperature by 26% [45]. The method test was conducted using measurements of body temperature with 30, 60, 90, and 120 min duration using DPT-HB induced.

Toxicity

Mice induced intraperitoneally with 0.7 g/kg BW of PC leaves ethanol extract did not exhibit acute toxicity. [43]. In the test method, each animal was given an extract with an intraperitoneal injection (I. P.) on the first daytime of the test. Every dose was given in 0.2 ml of a 0,1% CMC solution. One group, treated as the control group, received a CMC solution. The level of toxicity was found by seeing if the mice were still alive seven days after being given the extract.

Anti-inflammatory

According to [47], At a concentration of 15%, the extract was able to suppress inflammation by 87.78% and reduced exudate volume by 46.67±5.506 µl. Ethanol extract from PC leaves significantly affected the number of lymphocytes, stem neutrophils, and segment neutrophils but not the number of monocyte cells. Ethanol extract of PC leaves at a concentration of 15% obtained, lymphocyte cells value was 50.11±2.389, stem neutrophil cells value was 10.44±0.475%, segmented neutrophil cells value was 19.78±0.596, and monocyte cells value was 2.0±0.025%. Anti-inflammatory activity was investigated using two test methods: generating granuloma sacs and making edema on the back of mice, which had previously been administered 2% carrageenan subcutaneously. According to [46], subjects induced by carrageenan and then given extract ethanol with a concentration of 15% could reduce exudate volume by 46.67±5.506 µl and suppress inflammation by 87.78%.

Antiparasitic

The extract was administered intraperitoneally to each animal test on the first day of the experiment. Each dose was administered in 0.2 ml of CMC solution containing 0.1% carboxymethyl cellulose. One group served as the control given the CMC solution. At an intraperitoneal dose of 0.7 µg/kg BW, PC showed significant antiparasitic activity with IC_{50} values ranging from 5.3 to 49.3 µg/ml and without acute toxicity in mice [43].

In vitro and *In vivo* immunomodulatory and anti-inflammatory activities of PC extract have been reported. However, the mechanism of PC as immunomodulatory and anti-inflammatory was not yet studied. In addition, not many phytochemical constituents isolated from PC that explored. So it is highly recommended for further experimental research to study the immunomodulatory and anti-inflammatory mechanisms of a phytochemical constituent in PC extract.

CONCLUSION

Traditional medicine PC is used to treat various diseases such as increasing the stamina of hard workers, toothache, malaria, fever, skin diseases, refreshing drinks, itching, bruises, and curing high blood pressure, and as such, food ingredients.

The Phytoconstituent of PC was Peronemin A2, A3, B1, B2, B3, C1, and D1. It also contains phenols, triterpenoids, flavonoids, tannins, alkaloids, steroids, saponins, alkanes, alcohol, and fatty acid.

The pharmacological action of PC is immunomodulatory, anti-inflammatory, tyrosinase inhibitory, glucosyltransferase inhibitory, antiplasmodial, photo cytotoxic, antibacterial, antidiabetic, antiplasmodial, antioxidant, anticancer (cytotoxic activity), and non-teratogenic. *In vitro* and *In vivo* of PC activity is immunomodulatory and anti-inflammatory. *In vivo* studies are antiparasitic, antipyretic, immunomodulatory, anti-inflammatory, antidiabetic, and antihyperuricemia, with no toxic effect.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

Declared none

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