

Reactualiting *Phanera semibifida* (Roxb.) Benth. from Sumatra, Indonesia as an Anticancer Agent and Phylogenetic Position

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ABSTRACT

The increasing prevalence of cancer worldwide demands the intensification of efforts to develop natural solutions for its treatment. Herbal plants have provided a strong evident base in treating of this disease in many indigenous tribes in the world. *Phanera semibifida* has been widely used as a viable anti-degenerative drug for cancer treatment. This study reviews selected plant species with taxonomy status, phylogeny position, phytochemistry and pharmacology study based on a author's research and literature review conducted through relevant keyword searches in databases, Web of Science, Scopus, PubMed, and Google Scholar. Detailed analysis of research studies proves that *P. semibifida* can be used as an anticancer agent with strong basic evidence based on indigenous knowledge from traditional communities.

Key words: Anticancer, Leguminosae, *Phanera semibifida*, Pharmacology, Sumatra.

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INTRODUCTION

In the human body, free radicals are considered to play a role in the process of disease. The imbalance between the content of free radicals and antioxidants in the body becomes the dominant cause of free radicals, resulting in various diseases such as cancer, coronary heart disease, diabetes, liver and premature aging.^[1] Antioxidants are compounds that can prevent the occurrence of oxidation reactions of other compounds both in the body and for other compounds that are easily oxidized.^[2] Antioxidants are chemical compounds that can donate one or more electrons to free radicals, so that free radical can be reduced by their radical properties.^[3] Currently, exposure to free radicals is quite widespread in people's lives, such as pollution and lifestyle.^[4] Plants containing antioxidant compounds have an important role in increasing immunity in the body.^[5-8]

The immune system is the body's defense mechanism in charge of responding or responding to attacks from outside the body, such as bacteria, viruses, fungi, and various germs that cause disease.^[9,10] When the immune system does not work optimally, the body will be vulnerable to infection. Several things can affect the immune system, such as environment, food, lifestyle, stress, age, and hormones.^[11,12] Immunomodulator serves to develop materials that can enhance the immune response or restore the immune systems.^[13,14] Improving the immune system can be done in various ways, one of which is by consuming of supplements that function as immunomodulators.^[15-17]

Various diseases continue to undergo massive differentiation and quickly attack many people due to lifestyle changes. The lifestyle of consuming fast food and lack of activity can increase the risk of heart disease, stroke, diabetes, and cancer, which are better known as degenerative diseases. Based on WHO data degenerative diseases are the main cause of death globally with around 54%. The increasing prevalence of degenerative diseases such as cancer requires scientists to find new sources of natural ingredients as potential natural antioxidants.^[18-20]

Globally cancer is a disease that greatly affects the human population. Many scientific studies to find potential compounds from herbal plants as targets for potential anticancer treatments.^[21] Plants produce natural secondary metabolites that are being investigated for anticancer activity leading to new clinical drugs.^[22] Natural herbs have harmless side effects compared to current treatments such as chemotherapy.^[23]

Kangkang katup (*Phanera semibifida* (Roxb.) Benth.) has strong basic evidence in traditional Malay medicine in the Riau Islands, Sumatra, Indonesia. Previous studies have revealed that valve ribs are a source of antioxidants and immunomodulators.^[24,25] This evidence makes a major contribution to revealing the potential of natural resources as anticancer drugs. This review will explore the chemical diversity of *P. semibifida* which has potential as an anticancer with clear taxonomic and phylogenetic identity authentication.

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TAXONOMY OF PHANERA SEMIBIFIDA

Naming is the key to unlocking all information about an organism. If the name is not clear. The information about the organism is also invalid and not recognized by the scientific community. *Kangkang katup* (*Phanera semibifida*) is a herbal plant always present in every traditional medicinal herb, such as in the Riau Lingga Malay tribe, Riau Islands Province. A valid name is very important in developing the potential of plants as medicinal plants. *Phanera semibifida* (Roxb.) Benth is an accepted name by The International Plant Names Index (IPNI), basionym with *Bauhinia semibifida* Roxb. from Fabaceae (leguminosae: *Caesalpinioideae*). Originally *Phanera* was a subgenus of *Bauhinia*. However, it has been revised by de Wit,^[26] as the most recent genus in *Bauhinia* with specialization characters is nearly entirely composed of climbers and the presence of three fertile stamens.

***Phanera semibifida* (Roxb.) Benth.** in Miquel, *Pl. Jungh.* (1852) 263; Miquel, *Fl. Ind. Bat.* 1 (1855) 61; de Wit, *Reinwardtia* 3 (1956) 465 (Figure 1).^[26-28]

Perennial, woody climber. Leaves simple, butterfly-shaped (with bifoliate consisted of two leaflets), green and glabrous above. Petiole 2-6 cm, pubescent to glabrous. Lamina obovate-orbicular, 4-11 cm diam; (9-)11-13-nerved; bifid 1/4 - 2/5, tips of lobes rounded, base cordate, entire, curved; upper surface dark green, glabrous, lower light green, glabrous to glabrescent. Inflorescences start out white and age to yellow, fragrant, terminal, elongated erect racemes. Flower buds mature from fairly glabrous white to pubescent golden brown, opening sequentially from bottom to top. Calyx early splitting into 5 reflexed, strap-shaped sepals, 1-2.5 cm long. Petals white turning yellow, unequal, elliptic to oblong, glabrous except for the pubescent claw, and sometimes sparsely hirsute externally along the median line, 2-3(-3.5) cm long, claw 2-5 mm. Stamens 3 fertile; filaments 2.5-3 cm, glabrous, stout; anthers oblong, 1 cm, opening by a longitudinal slit; staminodes 2-3, small, filiform. Stipe of ovary c. 3 mm, ovary c. 10 mm, style stout, c. 5 mm, all entirely densely brown silky tomentose; style increasing towards the very large oblique, peltate stigma, up to 5 mm across, much lengthening after anthesis. Fruits like dried, woody, strap-straped, bean pods 10–20 by 3–4 cm. Each fruit bears up to 6 disc-like, flat seeds within.

Distribution: *P. semibifida* is a tropical plant with native distribution in Peninsular Malaysia, Myanmar, the Philippines, Borneo Sulawesi, and Sumatra.

Habitat: It grows along with open areas in forests, and forest edges up to 2000 m altitude

Vernacular names: Ganggang katup (Lingga); Kupu-kupu (Borneo, Pontianak); Takui lebang (Sungei); Akar kati katwi (Sumatra, Mt Ophir), Andor sibola ringring (Asahan), Bulun siduaja (Simalur), Akar pulalang (Jambi).

MOLECULAR PHYLOGENY ANALYSIS OF PHANERA SEMIBIFIDA

We collected two accessions of *Phanera semibifida* from Sumatra: Riau Islands and West Sumatra. The relatively closely related species was selected as the outgroup for phylogenetic analyses based on ITS sequences.^[29] DNA sequences of ITS region of species and outgroup taxa were aligned by Unipro UGENE.^[30] Maximum parsimony analysis was performed using PAUP*.^[31] Clade robustness was evaluated by bootstrap analysis using 1000 replicates of heuristic searches.^[32]

The result of BLAST indicated that two accession *P. semibifida* has a high similarity to *P. semibifida* (AY258395.1) with identity value $\geq 95\%$ while the similarity to both *P. nervosa* (HG004798.1) and *Bauhinia championii*

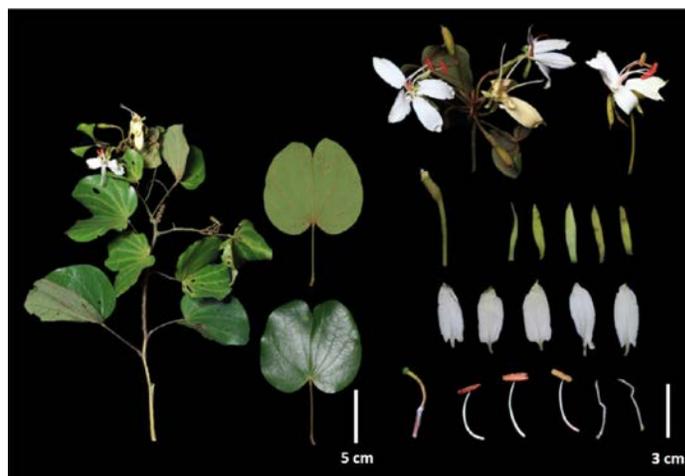


Figure 1: Morphological characters of *Phanera semibifida* grown in West Sumatra, Sumatra.

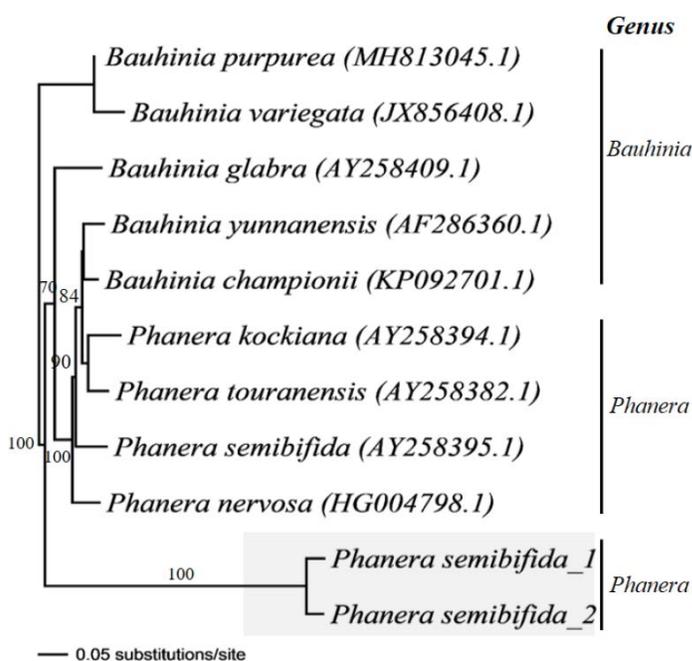


Figure 2: Cladogram of two species of *Phanera semibifida* as compared to related species based on ITS marker with the neighbour-joining method with bootstrap values 1000x. The numbers above lines represent bootstrap values in 1000 replicates. *P. semibifida_1* collected from Riau Islands, and *P. semibifida_2* collected from West Sumatra.

(KP092701.1) is less than 95% (Table 1). Using BLAST parameters are important to determine species name.^[33]

The phylogenetic tree of *P. semibifida* based on Internal Transcribed Species (ITS) markers sequences showed kinship with the genus *Phanera* and its relatives. Phylogenetic analysis is based on a representative sample of the genera *Phanera* and *Bauhinia*, including nine accessions taken from GenBank data. The phylogeny tree reveals two main clades, supported by a high bootstrap value. Two accessions of *P. semibifida* formed separate clusters from other species (Figure 2). Differences from environmental factors in their habitat can change nucleotides the basic constitution of the species,^[34] and the chemical components between

Table 1: BLAST analysis of ITS region sequences of species from Riau Islands and West Sumatra.

Description	Species	Max score	Total score	Query cover (%)	E value	Ident (%)	Accession
<i>Bauhinia semibifida</i> internal transcribed spacer 1, 5.8S ribosomal RNA gene, and internal transcribed spacer 2, complete sequence (common name: <i>Phanera semibifida</i>).	<i>P. semibifida_1</i>	1101	1101	87	0.0	99.02	AY258395.1
	<i>P. semibifida_2</i>	937	937	96	0.0	95.02	
<i>Lasiobema championii</i> 18S ribosomal RNA gene, partial sequence; internal transcribed spacer 1, 5.8S ribosomal RNA gene, internal transcribed spacer 2, complete sequence; and 28S ribosomal RNA gene, partial sequence (common name: <i>Bauhinia championii</i>).	<i>P. semibifida_1</i>	926	926	98	0.0	90.90	KP092701.1
	<i>P. semibifida_2</i>	800	800	96	0.0	88.05	
<i>Bauhinia nervosa</i> 18S rRNA gene, ITS1, 5.8S rRNA gene, ITS2 and 28S rRNA gene (common name: <i>Phanera nervosa</i>).	<i>P. semibifida_1</i>	918	918	98%	0.0	90.61	HG004798.1
	<i>P. semibifida_2</i>	880	880	96%	0.0	90.25	

P. semibifida_1 collected from Riau Islands, and *P. semibifida_2* collected from West Sumatra.

species that grow in different countries could vary due to climate and another geographic factor.^[6]

All of these segregate genera in *Bauhinia* based on trnL-F, and ITS region is monophyletic except for *Phanera*, which is divided into two lineages comprising the Asian *Phanera* species together with the genus *Lasiobema*, and the second containing the American *Phanera* species.^[35-37] *Phanera* is probably better recognized as two lineages, one comprising neotropical *Phanera*, corresponding to the genus *Schnella*, and the other containing the Asian *Phanera* and *Lasiobema* species. However, more sampling and more variable molecular markers are needed to resolve the taxonomic status of *Phanera* and *Lasiobema*.^[35]

Cladogram based on ITS region showed two accession *P. semibifida* from Sumatra identical to *P. semibifida* that grows in other countries. Based on the NJ analysis, the species collected from Sumatra were evolutionarily advanced because they had more extended branch sizes than other species collected from the GeneBank data. After all, they had more extended branch sizes. The genus *Phanera* differs from *Bauhinia* based on morphological and molecular characteristics. These findings are important in authenticating herbal plants for the development of pharmacological studies.

PHYTOCHEMISTRY OF PHANERA SEMIBIFIDA

The study about phytochemical of *Phanera* has known that these plants produce flavonoids,^[24,38,39] and stilbenoids.^[40-42] Phytochemical studies on one species of the genus *Phanera*, namely *P. semibifida*, two flavonoid compounds have been found that dominate. There were 6C-7O-dimethylaromadendrin (1), and phlorizin (2) (Figure 3) that have been isolated from the stem bark of *P. semibifida*. The flavonoid 4',5,7-trihydroxy-6,8-dimethylflavanone (farresol) and 3',4'-dihydroxy chalcone (isoliquiritigenin) together with triterpenoid (friedelin) were isolated from the aerial parts of *P. bracteata*.^[43] In general, a positive relationship appears to exist between total flavonoid content and antioxidant activity.^[44]

The difference in the flavonoid content of a plant is influenced by sunlight, an increase or decrease in sunlight affects the production of flavonoids. Enzyme activity in the formation of flavonoids in the photosynthesis process is highly dependent on sunlight. The higher the sunlight, the higher the transpiration rate. The photosynthesis results in carbohydrates are then processed in the cell to become flavonoid content in plants.^[45,46]

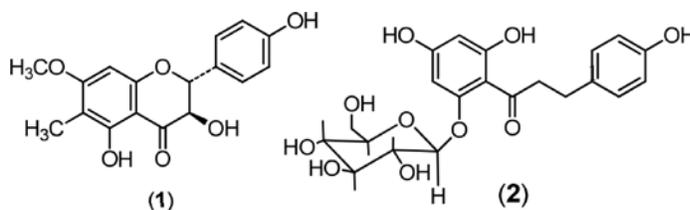


Figure 3: Structures of flavonoid isolated (1). 6C-7O-dimethylaromadendrin and (2) phlorizin.^[47]

Flavonoids are a group of phenolic compounds with antioxidant potential and play an important role in protecting against oxidative stress. Functional hydroxyl groups in flavonoids mediate their antioxidant effects by scavenging free radicals, and chelating metal ions.^[48] Flavonoids are one of the important components in nutraceuticals, pharmaceuticals and medicines. This is due to its antioxidant, anti-inflammatory, anti-mutagenic, and anti-carcinogenic properties coupled with its capacity to modulate cellular keys enzyme function.^[46]

PHARMACOLOGY OF OF PHANERA SEMIBIFIDA

Kangkang katup (*Phanera semibifida*) is one important component in Lingga Malay tribe herbal medicine,^[24] because it has high antioxidants. This species not only grows on the islands but can also be found in Riau mainland. Previous studies have revealed that valve ribs are a source of antioxidants and immunomodulators.^[2,25] This evidence significantly contributes to revealing the potential of natural resources as antidegenerative drugs due to changes in people's lifestyles known in certain tribal communities and other areas.

Antioxidant Activity

Antioxidants are a group of chemical compounds that can suppress cell damage caused by free radicals by giving electrons speedily and transforming the free radicals into stable forms to prevent oxidative damage that causes ailments.^[49] The presence of antioxidants in plants is primarily a protective compound from pests and disease, known as bioactive compounds. In this study, the quantitative phytochemical analysis was purposely conducted to determine the antioxidants and content of flavonoid and phenolic compounds, specifically gallic acid and quercetin. These analyses were performed using the DPPH method,

Table 2: Antioxidant activity in the root, stem bark and leaves of *P. semibifida*.

Organs	IC ₅₀ (ug/mL) Methanol	Antioxidant Activity Criteria*
Root	6.6247	Very strong
Stem bark	16	Very strong
Leaves	6.3486	Very strong

*Antioxidant activity criteria based on Zuhra.^[51]

and the concentration of gallic acid and quercetin were analyzed using HPLC.

As a traditional medicinal plant, all parts of *P. semibifida* have been tested for their antioxidant content, starting from the roots, stems, and leaves. Methanol extract obtained from maceration is rated to have an IC₅₀ value of 16 g/ml with an AAI value of 2.5, which is categorized as stronger than root and leaves (Table 2).^[50]

Based on the IC₅₀ value, the three *P. semibifida* plant organs can be used as medicinal herbs because they have high antioxidant activity. The community uses several genus *Bauhinia* and *Phanera* in traditional medicine, such as antitumor, bronchitis, dysentery, diabetes and antimicrobials.^[51-56] The part of the *Phanera* plant used as a herbal concoction is generally in the form of a decoction of root bark, stems and leaves.

Immunomodulator activity

Phanera semibifida was used by the traditional Malay community of Linga as a *Obat Pahit* herb. Every Traditional Medicine Practitioner (TMP) used this plant as a medicinal herb that was believed to be herbal medicine as a body energy keeper (immunomodulator and antioxidants).^[24] When the immune system works unwell, our body will be easily susceptible to disease infections.

This immunomodulatory effectiveness study has explored two aspects: activity and capacity of phagocytosis. Phagocytosis cells are predominantly important in the removal of bacteria and parasites from the body. They engulf these foreign bodies and degrade them using their powerful enzymes.^[57] Phagocytosis activity is the number of phagocyte cells ingesting antigens like bacteria, while phagocytosis capacity is the number of bacteria cells that are ingested by phagocytic cells.

P. semibifida extract showed an increase in phagocytosis against *Staphylococcus aureus* (SA) No. ATCC 12600 activity and phagocytic capacity to effectively modulate the immune system.^[25] *P. semibifida* extract can be used as an immunomodulatory raw material traditional knowledge-based herbal medicine. It also has potential as a standardized herb.

Anticancer Activity

Anticancer activity 6C-7O-dimethylaromadendrin and phlorizin using MTT assay has been widely used to assess cell viability. However, one must consider the enzymatic reduction of 3-[4,5-dimethylthiazole-2-yl]-2,5-diphenyltetrazolium bromide (MTT) to MTT-formazan is catalyzed by mitochondrial succinate dehydrogenase. Anticancer activity test against Murine leukemia P-388 cells showed IC₅₀ values of 2.76±0.08 ppm and 6.16±3.50 ppm. The IC₅₀ value obtained was included in the moderate and inactive activity categories. The cytotoxic activity of the ethyl acetate stem extract of *P. semibifida* obtained the IC₅₀ value of 72.93±0.01 ppm.^[58]

Anticancer activity assays were also proven in some relatives of *P. semibifida*, such as the flower of *P. kockiana* with gallic acid and methyl gallate that exhibited anticancer properties towards cancer cell lines.^[59] The antitumor potential of *Bauhinia variegata* against B16F10

melanoma tumor model in C57BL mice. The present investigation was undertaken to explore the antitumor activity of leaf, stem bark and flower extract of *Bauhinia variegata* against B16F10 melanoma tumor model in C57BL mice.^[60] The present study demonstrates the anticancer activity of extract *Bauhinia tomentosa*. The ethanol leaf extract of *B. tomentosa* has shown potent anticancer activity on A549 cancerous cell line. Further studies are needed to identify the bioactive molecules and explore their mechanism of action, which might throw light on the development of new alternative drugs for lung cancer.^[61,62] have reported the preparation of extracts from the various parts of *B. purpurea* leaves, stems, roots, and pods. These workers have isolated four new and very remarkable (dibenz[b,f]oxepins) cancer cell growth inhibitors and have designated them as Bauhiniastatins 1-4. The present study revealed that the phytochemicals in various *B. variegata* leaf extracts possess potent cytotoxic potential against human cancer cell lines.^[63]

An EtOH extract of *Bauhinia strychnifolia* showed good inhibitory activity against several cancer cell lines, including HT-29, HeLa, MCF-7, and KB. *Bauhinia strychnifolia* stem has compounds 2 and 3 on anticancer activity. Based on the anticancer activity of extracts and pure compounds isolated from it, this plant could be helpful in the treatment of cancer.^[38,64] The antiproliferative activity of specific plant lectins from seeds of *Bauhinia purpurea* appears to be due to the binding of lectins to the cell surface. It triggers the termination of the S and G2 phases. Induced apoptosis was found to be associated with LDH leakage, cell cycle arrest and, ROS generation. The apoptotic signal was amplified by caspase-3 activation resulting in cell death.^[65-67] This study proves that *P. semibifida* can be used as an anticancer agent and other antidegenerative diseases with strong basic evidence based on indigenous knowledge from traditional communities. Further research is needed to explore more of its active compounds and mechanisms of anticancer action to be used as standard herbal medicines.

CONCLUSION

Panera semibifida (Roxb.) Benth. (*Kangkang katup*) collected from Sumatra, Indonesia, have a variety of chemical content and pharmacological activity similar to *P. semibifida*, which grows in different areas. The genus *Phanera* differs from *Bauhinia* based on morphological and molecular characteristics. These findings are important in authenticating herbal plants for the development of pharmacological studies. Extracts from *P. semibifida* are rich in flavonoids exhibiting antioxidant and antidegenerative properties such as cancer. Anticancer properties have been proven in several studies inside and outside Indonesia. *P. semibifida* can be used as an anticancer agent and other antidegenerative diseases with solid basic evidence based on indigenous knowledge from traditional communities.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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