Journal of Pharmacy

REVIEW ARTICLE

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A Comprehensive Review on the Phytochemical Constituents, Antioxidant and Anticancer Properties of *Piper sarmentosum*

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ABSTRACT

Introduction: *Piper sarmentosum* is a herbaceous plant that belongs to the Piperaceae family and possesses antioxidant and anticancer properties due to its phytochemical compositions. It grows abundantly in Southeast Asia and is widely explored in the ethnomedicinal study.

Method: This paper reviews previous scientific research data on *P. sarmentosum* on its phytochemical constituents and antioxidant and anticancer properties. Related scientific articles were searched through academic search engines, including Elsevier, Science Direct, Google Scholar, and IOP Scinotes, where the literatures were reviewed thoroughly.

Results: The findings from the study have concluded that *P. sarmentosum* contains essential oils and flavonoids. Extensive reports on its antioxidant potential were also recorded, where *P. sarmentosum* was found to reduce free radicals. Researchers discovered that anticancer activities were exhibited against several cancer cell lines, including HepG2, HT-29, MCF-7, HeLa, MDA-MB-231, and HK-1. From the studied literatures, it can be concluded that the phytochemicals in *P. sarmentosum* contribute to its antioxidant and anticancer properties.

Conclusion: This research provides comprehensive and updated information on *P. sarmentosum*'s phytochemical constituents. These antioxidant and anticancer properties and antioxidant and anticancer properties that could be used as references for further investigation of *P. sarmentosum* in the pharmacological study.

ARTICLE HISTORY:

Received: 24 April 2022
Accepted: 1 July 2022
Published: 31 July 2022

KEYWORDS:

Piper sarmentosum, Phytochemical, Antioxidant, Anticancer, Ethnomedicine

HOW TO CITE THIS ARTICLE:

Ibrahim, M. A., Zulkiflee, N. F. I., & Mohd Hasali, N. H. (2022). A Comprehensive Review on the Phytochemical Constituents, Antioxidant and Anticancer Properties of *Piper sarmentosum*. *Journal of Pharmacy,* 2(2), 107-121.

doi: 10.31436/jop.v2i2.152

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Introduction

Piper sarmentosum is a type of herb plant that is mainly found in Southeast Asia, India, and Africa (Wei et al., 2019). This traditional medicinal plant was used as remedies in the Ayurvedic, Latin American and West Indies medicines (Salleh et al., 2012). *P. sarmentosum* is a dioecious erect shrub plant that grows up to 1.5m tall. The stem is swollen at the nodes. The leaves vary in size and shape; commonly heart-shaped, and alternately arranged. The flowers are tiny, and sessile without sepal (Raman et al., 2012). The plant is perceived as marketable and healing (Chaveerach et al., 2006). In Malaysia and Indonesia, known as "kaduk", the leaves and roots are used to treat headaches, coughs, asthma, and fungal infections (Chan & Wong, 2014). P. Sarmentosum's leaves are edible and they are widely exploited in pharmacological activities due to the presence of bioactive compounds. These compounds exhibit many bioactivities which include anticancer, antioxidant, antibacterial and antiinflammatory activities (Atiax et al., 2011; Chanwitheesuk et al., 2005; Zainal Ariffin et al., 2009). The aim of this study is to provide a comprehensive and up-to-date review focusing on the phytochemical contents of *P. sarmentosum*, as well as its antioxidant and anticancer properties. The literatures gathered from academic search engines were extensively reviewed and studied to summarize the latest data and information on the subjects. This review is essential as reference for future studies related to *P. sarmentosum*'s phytochemical components, antioxidant, and anticancer properties. An understanding of the pharmacological aspects of *P. sarmentosum*, especially its phytochemical constituents toward antioxidant and anticancer properties, could provide information on potential herbal medicine.

PHYTOCHEMICAL COMPOUNDS IN P. SARMENTOSUM

There are more than 100 phytochemicals, including essential oils, flavonoids, alkaloids, and steroids, that have been identified from *P. sarmentosum* (Hematpoor et al., 2018; Hieu et al., 2014; Qin et al., 2010; Rameshkumar et al., 2017; Syed Ab Rahman et al., 2016). Alkaloids and essential oils are the major constituents mainly extracted from the aerial sections and leaves of *P. sarmentosum*, while others have also been observed to be present in fruits and roots (Hematpoor et al., 2018; Rameshkumar et al., 2017).

Essential Oil

Essential oils are volatile phytochemical compounds that are mainly comprised of sesquiterpenes and phenylpropanoids (Ludwiczuk et al., 2017). According to Chanprapai & Chavasiri (2017) and Ludwiczuk et al. (2017), essential oils contain many bioactive compounds that are responsible for pharmacological activities. The *Piper* genus is known for its essential oil that as reported by Chaveerach et al. (2006), Salleh et al. (2012), and Zainal Ariffin et al. (2009). Qin et al., (2010) recorded the presence of 41 compounds from *P. sarmentosum* leaves through gas GC-MS analysis, which comprised of sesquiterpenes, monoterpenes, phenylpropanoids and alkane compounds that provide essential oils. Hieu et al., (2014) identified 19 phytochemicals of essential oils isolated from *P. sarmentosum* leaves which are mainly constructed as aromatic compounds. In addition, 11 compounds were isolated via GC-MS analysis for essential oils obtained from the fruits, leaves and roots of *P. sarmentosum* in a research conducted by Rameshkumar et al. (2017). Nugroho et al., (2020) identified six terpenoid compounds via GC-MS analysis of essential oil of *P. sarmentosum*. Sakilan et al. (2019) identified 17 compounds from the oils of *P. sarmentosum* obtained from ethanolic extraction and GC-MS. Table 1 lists out the essential oil isolated from *P. sarmentosum*.

Terpenoids

Terpenoids can be found in many plant products. It is build-up of isoprene unit (5C). It is classified by the number of isoprene unit (Ludwiczuk et al., 2017). Volatile oil of *P. sarmentosum* is rich in terpenoids component such as sesquiterpenes [**1-23**], and monoterpenes [**24-31**]. Sesquiterpenes are three 15C isoprene units coupled in a head-tail or non-head-tail arrangement (Ludwiczuk et al., 2017). Sesquiterpenoids have been reported to be one of the most abundant compounds that were present in *Piper* species (Rameshkumar et al., 2017). Previous studies reported that extracts with high amount of sesquiterpenes exhibit many bioactivities such as anti-inflammatory, herbicidal, insecticidal, fungicidal, and antibacterial (Hematpoor et al., 2016; Qin et al., 2010; Sharifah Farhana et al., 2014; Sun et al., 2020). Monoterpenes are made up of two isoprene backbone. Monoterpene can be either acyclic, monocyclic or bicyclic (Ludwiczuk et al., 2017). Chanprapai & Chavasari (2017) reported that GC-MS analysis of the essential oil of *P. sarmentosum* found that myristicin [**38**] has the highest composition at 27.27% followed by *trans*-caryophyllene **[21]** and α-copaene **[1]** at 18.03% and 10.40% respectively as stated in Table 1. Qin et al., (2010) also identified compound of **38** and **21** as significant components in the essential oil of *P. sarmentosum* at 65.22% and 13.89%. Myristicin showed antimicrobial activity against bacteria and fungi such as *Rhizoctonia solani*, *Bipolaris oryzae*, and *Xanthomonas oryzae* (Chanprapai & Chavasiri, 2017; Rameshkumar et al., 2017).

Phenylpropanoids

Phenylpropanoids [**40-46**] were also reported to be present in the essential oils of *P. sarmentosum*. Phenylpropanoids are plant compounds derived from the shikimate pathway and an important secondary metabolite

Table 1: Essential oils in *P. sarmentosum*.

No.	Compound	Source	Reference
1.	α-copaene	Leaf	(Chanprapai & Chavasiri, 2017; Hieu et al., 2014; Qin et al., 2010; Rameshkumar et al., 2017)
2.	α-humulene	Leaf; Fruit	(Chanprapai & Chavasiri, 2017; Hieu et al., 2014; Qin et al., 2010; Rameshkumar et al., 2017)
3.	α-ylangene	Leaf	(Hieu et al., 2014)
4.	α -cadinene	Leaf	(Chanprapai & Chavasiri, 2017; Qin et al., 2010)
5.	β-cadinene	Leaf	(Chanprapai & Chavasiri, 2017; Qin et al., 2010)
6.	β -cubebene	Leaf	(Chanprapai & Chavasiri, 2017;Rameshkumar et al., 2017; Sakilan et al., 2019)
7.	α -cadinol	Leaf	(Chanprapai & Chavasiri, 2017)
8.	β -eudesmol	Leaf	(Hieu et al., 2014)
9.	(*E*)-Nerodiol	Leaf	(Hieu et al., 2014)
10.	β -caryophyllene	Leaf; Stem	(Nugroho et al., 2020; Qin et al., 2010)
11.	Myrcene	Leaf	(Qin et al., 2010)
12.	Germacrene B	Leaf; Fruit; Root	(Rameshkumar et al., 2017)
13.	Germacrene D	Leaf; Stem	(Nugroho et al., 2020; Qin et al., 2010; Sakilan et al., 2019)
14.	Bicyclogermacrene	Leaf; Fruit; Root	(Rameshkumar et al., 2017)
15.	Cis-caryophyllene	Leaf	(Qin et al., 2010)
16.	Elemol	Leaf; Fruit; Root	(Rameshkumar et al., 2017)
17.	β-eudesmol	Leaf	(Hieu et al., 2014)
18.	Cadinol	Leaf	(Qin et al., 2010)
19.	Biocyclogermacrene	Leaf	(Qin et al., 2010)
20.	Cis-caryophyllene	Leaf	(Qin et al., 2010)
21.	Trans-Caryophyllene	Leaf	(Chanprapai & Chavasiri, 2017; Sakilan et al.,2019)
22.	γ-eudesmol	Leaf; Fruit	(Chanprapai & Chavasiri, 2017)
23.	(-)-alloaromadendrene	Leaf	(Qin et al., 2010)
24.	Cedarene	Leaf	(Qin et al., 2010)
25.	β -elemene	Leaf	(Qin et al., 2010)
26.	Valencene	Leaf; Fruit	(Chanprapai & Chavasiri, 2017)
27.	α -pinene	Leaf	(Hieu et al., 2014; Qin et al., 2010)
28.	Limonene	Leaf	(Chanprapai & Chavasiri, 2017; Qin et al., 2010)
29.	Linalool	Leaf	(Hieu et al., 2014; Qin et al., 2010)

Table 1: Essential oils in *P. sarmentosum* (cont.).

No.	Compound	Source	Reference
30.	Nerol	Leaf	(Hieu et al., 2014; Qin et al., 2010)
31.	Myrcene	Leaf	(Chanprapai & Chavasiri, 2017; Qin et al., 2010)
32.	Trans-β-ocimene	Leaf	(Chanprapai & Chavasiri, 2017; Qin et al., 2010)
33.	Terpene	Leaf	(Qin et al., 2010)
34.	α-thujene	Leaf	(Qin et al., 2010)
35.	β-pinene	Leaf	(Chanprapai & Chavasiri, 2017; Qin et al., 2010)
36.	β-asarone	Leaf	(Bactiar & Fahami, 2019)
37.	(E)-Cinnamic acid	Leaf	(Hieu et al., 2014)
38.	Myristicin	Leaf; Fruit	(Bactiar & Fahami, 2019; Qin et al., 2010; Rameshkumar et al., 2017)
39.	Terpinen-4-ol	Leaf; Fruit	(Chanprapai & Chavasiri, 2017)
40.	Isosarone	Root	(Hematpoor et al., 2018; Qin et al., 2010)
41.	Trans-asarone	Root	(Hematpoor et al., 2017; Qin et al., 2010)
42.	Safrole	Leaf	(Chanprapai & Chavasiri, 2017; Qin et al., 2010)
43.	Apiole	Fruit; Root	(Rameshkumar et al., 2017)
44.	Elemicin	Leaf; Fruit; Root	(Chanprapai & Chavasiri, 2017; Qin et al., 2010; Rameshkumar et al., 2017)
45.	Benzyl alcohol	Leaf	(Hieu et al., 2014)
46.	Asariscin	Root	(Hematpoor et al., 2018)
47.	γ-terpinene	Leaf	(Hieu et al., 2014)
48.	Eicosane	Leaf	(Hieu et al., 2014)
49.	Pipataline	Root; Fruit	(Rameshkumar et al., 2017)
50.	Docosane	Leaf	(Chanprapai & Chavasiri, 2017; Hieu et al., 2014)
51.	Phytol	Leaf; Stem	(Hieu et al., 2014; Nugroho et al., 2020; Qin et al., 2010; Sakilan et al., 2019)
52.	Apiole	Fruit	(Rameshkumar et al., 2017)
53.	Naringenin	Leaf	(Bactiar & Fahami, 2019)
54.	β-asarone	Leaf	(Bactiar & Fahami, 2019; Qin et al., 2010)
55.	Benzyl benzoate	Leaf	(Hieu et al., 2014)
56.	Trans-2-butenyl Benzene	Leaf	(Hieu et al., 2014)
57.	Hexacosane	Leaf; Fruit	(Chanprapai & Chavasiri, 2017)
58.	Heptacosane	Leaf; Fruit	(Chanprapai & Chavasiri, 2017)
59.	Tricosane	Leaf; Fruit	(Chanprapai & Chavasiri, 2017)
60.	Tetracosane	Leaf; Fruit	(Chanprapai & Chavasiri, 2017)

in plants. It is derived from parent compounds with C6-C3 units as its core. The derivatives are synthesized through cinnamic acid pathway (Seigler, 1998). Bioassay-guided fractionation of the extracts of *P. sarmentosum* showed that phenylpropanoids isolated from *P. sarmentosum* exhibit notable herbicidal and fungicidal properties (Hematpoor et al., 2017, Hematpoor et al., 2016; Hematpoor et al., 2018). Asariscin [**46**], isosarone [**40**] and trans-asarone [**31**] had been reported to have toxicity effect against *Sitophilus oryzae, Plodia interpunctella* and *Rhyzopertha dominica* (Hematpoor et al., 2016, 2017). Other compounds such as benzyl alcohol [**34**], benzyl benzoate [**44**] and trans-2-butenyl benzene [**45**] were reported to be the highest in essential oils of *P. sarmentosum* at 17.9%, 49.1% and 7.9% (Hieu et al., 2014).

Flavonoids

Flavonoids are classified as phenolic compounds which are naturally found in plants. Based on previous research and study, flavonoid contents of plants had been associated with the plant pharmacology such as antioxidant, antihypertensive, antibacterial, and antifungal. Table 2 shows the flavonoid contents of P. sarmentosum recorded from multiple previous studies. Ugusman et al., (2012) reported that the total flavonoid content of P. sarmentosum aqueous extract is 48.57 ± 0.03 mg GAE/g DM. Further analysis using HPLC exhibited the occurrence of flavonoid rutin [62] and vitexin [61] as the core flavonoid content of the aqueous extract of *P. sarmentosum*. Next, Bactiar & Fahami (2019) identified 15 phytochemical compounds isolated from fresh leaves of *P. sarmentosum* which included four flavonoid compounds didymin **[63]**, naringenin **[64]**, hesperidin **[65]**, and quertecin **[66]**. Through bioassay guided fractionation of the chloroform extract of *P. sarmentosum*. Pan et al., (2011) identified four benzylated hydrocarbons; sarmentosumins A-D together with 14 other compounds.

Alkaloids are secondary metabolite compounds that contain at least one nitrogen atom in its structure. The N atom is usually located in the ring structure. Alkaloids can be classified as indole, quinolines, isoquinolines, pyrrolidines, pyridines, pyrrolizidines, tropanes, and steroids (Kurek, 2019). As shown in Table 3, the genus Piper was reported to contain many alkaloid compounds mainly the amide alkaloid (Perez Gutierrez et al., 2013). Bactiar & Fahami (2019) isolated few alkaloid compounds from the methanolic leaf extract of P. sarmentosum using LC-MS. Alkaloid compounds such as amurensin [76], guineensine [77], and malvidin [78] were reported to exhibit bioactivities such as anti-inflammatory, antihypertensive and analgesic (Bactiar & Fahami, 2019). Shi et al., (2017) reported the presence of amide alkaloids from the aerial parts of P. sarmentosum through a process

Table 2: Flavonoids in *P. sarmentosum*.

No.	Compound	Source	Reference
61.	Vitexin	Leaf	(Ismail et al., 2018; Ugusman et al., 2012)
62.	Rutin	Leaf	(Bactiar & Fahami, 2019; Ismail et al., 2018; Ugusman et al., 2012)
63.	Didymin	Leaf	(Bactiar & Fahami, 2019)
64.	Naringenin	Leaf	(Bactiar & Fahami, 2019)
65.	Hesperidin	Leaf	(Bactiar & Fahami, 2019)
66.	Quertecin	Leaf	(Bactiar & Fahami, 2019)
67.	Sarmentosumin A	Aerial part	(Pan et al., 2011)
68.	Sarmentosumin B	Aerial part	(Pan et al., 2011)
69.	Isochamanetin	Aerial part	(Pan et al., 2011)
70.	Sarmentosumin C	Aerial part	(Pan et al., 2011)
71.	Sarmentosumin D	Aerial part	(Pan et al., 2011)
72.	Dichamentin	Aerial part	(Pan et al., 2011)
73.	7-methoxy dichamanetin	Aerial part	(Pan et al., 2011)
74.	Pinocembrin	Aerial part	(Pan et al., 2011)
75.	7-methoxy chamanetin	Aerial part	(Pan et al., 2011)

Table 3: Alkaloids in *P. sarmentosum*.

No.	Compound	Source	Reference
76.	Amurensin	Leaf	(Bactiar & Fahami, 2019)
77.	Guineensine	Leaf	(Bactiar & Fahami, 2019)
78.	Malvidin	Leaf	(Bactiar & Fahami, 2019)
79.	Piperflaviflorine	Aerial part	(Shi et al., 2017)
80.	Sarmentamide B	Aerial part	(Shi et al., 2017)
81.	Brachyamide B	Leaf; Aerial part	(Bactiar & Fahami, 2019; Shi et al., 2017)
82.	Pellitorine	Aerial part	(Pan et al., 2011; Shi et al., 2017)
83.	Homopellitorine	Aerial part	(Shi et al., 2017)
84.	Piperyline	Aerial part	(Shi et al., 2017)
85.	Sarmentine	Aerial part	(Shi et al., 2017)
86.	Dimethoxypiplartine	Aerial part	(Shi et al., 2017)
87.	Brachystamide B	Leaf; Fruit	(Bactiar & Fahami, 2019)
88.	Langkamide	Root; Shoot	(Bokesch et al., 2011)
89.	3,4,5-Trimethoxy cinnamicacid	Root; Shoot	(Bokesch et al., 2011)
90.	Piplartine	Root; Shoot	(Bokesch et al., 2011)

of repeated column chromatography. Aside from common amide compounds observed in *Piper* species, sarmentamide B **[80]** and piperflaviflorine **[79]** were identified as new alkaloid compounds observed in *P. sarmentosum*. Through spectroscopic analysis, both compounds showed antifungal and antibacterial activity (Shi et al., 2017). Brachyamide B **[81]** is a minor amide alkaloid that has been observed in most *Piper* species (Bactiar & Fahami, 2019; Shi et al., 2017).

Other compounds

Previous studies found a variety of other chemicals in *P. sarmentosum*, as listed in Table 4. Using analytical instrumentation of Mass spectrometry (MS) and Nuclear Magnetic Resonance (NMR), six novel chemicals, sarmentosumols A to F **[93-98]**, were discovered from the ground section of *P. sarmentosum* (Yang et al., 2013). The sarmentosumols were tested and reported to exhibit strong antimicrobial activity against *S. aureus* with 7.0 g/mL minimum inhibition concentration (MIC). Next, other different compounds reported included difucol **[91]**, methyl piperate **[92]**, pellitorine **[99]**, pipercallosine **[101]** and sesamin **[102]** (Bactiar & Fahami, 2019; Pan et al., 2011; Yang et al., 2013). According to Hussain et al., (2009), the compounds that exist in the extracts play a significant role in the plant's bioactivities.

ANTIOXIDANT PROPERTIES OF P. SARMENTOSUM

Many investigations have discovered that *P. sarmentosum* extracts exhibit antioxidant properties, with varied effects on different parts of the plant. These antioxidant properties were related to the total flavonoid and phenolic contents (Chanwitheesuk et al., 2005; Lee et al., 2014; Wei et al., 2019; Yeo et al., 2018). Compounds such as alkaloids, amides and carotenes were also reported to exhibit antioxidant activity. Different studies including chemical assays, *in vitro* and *in vivo* studies have been reported to evaluate the antioxidant properties of *P. sarmentosum* extracts. *In vivo* animal studies have been reported which utilized Wistar rats, Yarkshire piglets, Sprague Dawley rats and albino mice (Azlina et al., 2011; Mohd Zainudin et al., 2015; Wang et al., 2017). Different cell cultures have been used for the *in vitro* antioxidant studies such as murine monocytic macrophages cell lines (RAW 264.7), human umbilical vein endothelial cells (HUVEC), human neuroblastoma cells (SH-SY5Y) and immortalized murine microglial cells (BV-2) (Langyanai et al., 2017; Ugusman et al., 2012; Yeo et al., 2018). There are several chemical antioxidant assays

Table 4: Other compounds in *P. sarmentosum*.

No.	Compound	Source	Reference
91.	Difucol	Leaf	(Bactiar & Fahami, 2019)
92.	Methyl piperate	Leaf	(Bactiar & Fahami, 2019)
93.	Sarmentosumols A	Aerial part	(Yang et al., 2013)
94.	Sarmentosumols B	Aerial part	(Yang et al., 2013)
95.	Sarmentosumols C	Aerial part	(Yang et al., 2013)
96.	Sarmentosumols D	Aerial part	(Yang et al., 2013)
97.	Sarmentosumols E	Aerial part	(Yang et al., 2013)
98.	Sarmentosumols F	Aerial part	(Yang et al., 2013)
99.	Pellitorine	Aerial part	(Pan et al., 2011)
100.	Pipercallosidine	Aerial part	(Pan et al., 2011)
101.	Pipercallosine	Aerial part	(Pan et al., 2011)
102.	Sesamin	Aerial part	(Pan et al., 2011)

used for the research of antioxidant properties of *P. sarmentosum*. Assays involved includes DPPH scavenging assay, B- carotene linoleate (BCL) assay, superoxide scavenging (SOSc) assay, FRAP assay or ion chelating activity (ICA), and hydroxyl radical scavenging (HRS) assay (Chanwitheesuk et al., 2005; Langyanai et al., 2017; Mohd Zainudin et al., 2015; Wei et al., 2019). Utilization of biochemical parameters such as malondialdehyde (MDA), glutathione peroxidase (GPX), superoxide dismutase (SOD), cell viability, and thiobarbituric acid reactive substances (TBARS) were also included to measure the antioxidant activities of *P. sarmentosum* extracts (Azlina et al., 2011; Mohd Zainudin et al., 2015; Wang et al., 2017).

The extracts of all parts of *P. sarmentosum* showed antioxidant activity, which varied depending on the solvent used in the extraction. As reported by Lee et al., (2014), the methanol extract of *P. sarmentosum* leaves yielded higher antioxidant activity than the hexane, chloroform, butanol, aqueous, and ethyl acetate extracts. Another study by Yeo et al., (2018) also revealed that methanol extract had the highest antioxidant activity, followed by hexane, dichloromethane, and ethyl acetate. Other solvents that have been used in the extraction of *P. sarmentosum* are ethanol, water, and carbon dioxide (using supercritical fluid extraction method). Table 5 summarizes of the antioxidant activity of *P. sarmentosum* from previous literature and studies.

In Vivo and In Vitro Antioxidant Properties

As displayed in Table 5, the most common chemical assay used in the antioxidant evaluation of *P. sarmentosum* was DPPH scavenging assay. DPPH is a constant radical due to the resonance of nitrogen oxide group in the picryl moiety and the electrical balance in hydrazine group in the molecule structure. With the addition of antioxidant chemicals, DPPH radicals were reduced, resulting in a colorless solution, making it easier to assess a substance's antioxidant qualities. This method has been used as standard in most food antioxidant capacity. Table 5 depicted that extracts of *P. sarmentosum* were able to neutralize DPPH compound. Wei et al., (2019) reported that ethanolic extract of *P. sarmentosum* able to reduce ferric compound with FRAP value of 0.28, 0.79 and 0.85 µmol/mL. FRAP assay, which is also known as ICA is a method used to observe the antioxidant capability of a compound via the ferric reducing ability from Fe^{3+} to Fe^{2+} (Ismail et al., 2018). The method was deemed to be reliable to calculate the antioxidant capacity of a sample. Other assays such as the SOSc and HRS utilized the same concept as both DPPH and FRAP assays where the antioxidant ability was measure through the reducing capabilities of the compounds (Ismail et al., 2018). Wongsa et al., (2012) and Chanwiteesuk et al. (2006) utilized the BCL assay to measure the antioxidant capacity of *P. sarmentosum*. Studies showed that both exhibit antioxidant activity with antioxidant activity index (AAI) of 13.0±0.84 and 1.11±0.00, respectively (Chanwitheesuk et al., 2005; Wongsa et al., 2012). The AAI is the measurement of the bleaching rate of control against the bleaching rate of sample (Chanwitheesuk et al., 2005; Ueno et al., 2014).

In vivo and *in vitro* of antioxidant evaluation of *P. sarmentosum* were observed and tested against different animal model and cell lines. In these studies, biochemical parameters were utilized. TBARS and MDA are the common parameters used in the *in vivo* and *in vitro*

Table 5: Summary for antioxidant studies of *P. sarmentosum*.

No.	Studies conducted	Plant part	Solvent	Result	Reference
1.	Chemical assays performed. Antioxidant activity of *P. sarmentosum* from three different regions in China tested using DPPH and FRAP. TPC was also determined.	Leaves	Ethanol	Scavenging ability of *P. sarmentosum* extracts were at 42.61%, 88.65% and 82.78%. *P. sarmentosum* extract reducediron ions at 0.28, 0.79 and 0.85 µmol/mL. The TFC of each sample is different.	(Wei et al.,2019)
2.	Chemical assays performed. B-carotene bleaching (BCL) assays performed to test the antioxidant activity. TVC, TVE, TXC, TTC and TPC were determined.	Leaves	Methanol	Extracts exhibited highest antioxidant index at 13.0±0.84Antioxidant compounds were determined.	(Chanwitheesuk et al., 2005)
3.	Chemical assays performed. Antioxidant properties determined by the *in vitro* AChE inhibitory and DPPH	Whole plants	Methanol	Extracts showed moderate AChE inhibition activity at 31.42±2.36% Extracts showed good DPPH scavenging ability at 51.47%	(Langyanaiet al., 2017)
4.	Chemical assay performed. Antioxidant properties determined through DPPH assay. TPC and TFC were also determined.	Leaves	Methanol, aqueous, hexane, chloroform, ethyl acetate, butanol	Antioxidant activity observed by *P. sarmentosum* methanol extract with EC_{50} value of 2.70±0.3 mg/mL. The TPC and TFC of methanol extract is higher compared to hexane, chloroform, aqueous, ethyl acetate and butanol.	(Lee et al.,2014)
5.	Chemical assays and *in vivo* animal studies for 28 days. Wistar rats divided in five groups which are normal, spontaneous hypertensive and three of hypertensive rats. Antioxidant capabilities tested through DPPH assay,SOSc assay, and serum MDA.	Leaves	Aqueous	The antioxidant activity was at 96.21±0.88% for DPPH and 95.69±0.18% for SOSc. Reduction of serum MDA observed in hypertensive ratstreated with *P. sarmentosum*.	(Mohd Zainudin etal., 2015)
6.	Chemical assay and *in vitro* cell culture study. Antioxidant properties determined through DPPHassay. TPC was also determined.	Leaves	Hexane, methanol, dichloromet hane, ethyl acetate	Highest DPPH scavenging reported for methanol extract followed by hexane, DCM andethyl acetate. Correlation between the antioxidant properties and the TPCis not clear	(Yeo et al.,2018)

Table 5: Summary for antioxidant studies of *P. sarmentosum* (cont.).

No.	Studies conducted	Plant part	Solvent	Result	Reference
7.	*In vivo* animal study Four random groups of 21 days old, Duroc Landrace- Yorkshire piglets formed. Antioxidant properties measured using lung serum MDA and GPX activity.	Stem and leaves	Supercritic alcarbon dioxide	Increase of GPX and decrease in MDA observed in piglets treated with *P. sarmentosum*.	(Wang etal., 2017)
8.	*In vivo* animal study. 28 days old of 32 Wistarrats divided randomly groups of eight. Antioxidant properties were measured using plasma TBARS and lungTBARS, GPX and SOD activity.	Leaves	Methanol	Decline in lung TBARS and GPXactivity in rats supplied with *P. sarmentosum*.	(Azlina etal., 2011)
9.	*In vitro* cell culture study. HUVECused for study of cytoprotective *P. sarmentosum* against oxidative stress.Antioxidant properties determined through MTT assay. TPC and TFC were alsodetermined	Leaves	Aqueous	Extract was effective in increasing the viability of H_2O_2-induced HUVEC. Aqueous extract of *P. sarmentosum* contained high TFCand TPC.	(Ugusman et al., 2012)
10.	Chemical assay study. Antioxidant properties determined using DPPH and BCL assay. TPC was determined.	Leaves	Aqueous	DPPH scavenging ability of *P. sarmentosum* was 46.84 ± 0.30% inhibition and BCl protection factor of 1.11 ± 0.00. TPC of the extract was 10.98 ± 0.25 mg GAE/g /dw	(Wongsa etal., 2012)
11.	Chemical assay study. Antioxidant activity measured using DPPH andNO inhibition assay. TPC was determined.	Leaves	Methanol	Extract showed DPPH and NO scavenging ability with IC_{50} of 129.65 ± 1.04 and 60.24 ± 2.39. The TPC of extract was 50.01 mg GAE/g /dw.	(Lee et al., 2011)
12.	Chemical assay study. Antioxidant activity measured using DPPHassay. Phytochemical contents of extract were determined.	Leaves	Ethanol	55.25ppm of ethanol extract reduced DPPH by 50%. Presence of alkaloids, flavonoids, steroids, and saponins were reported.	(Sakilan etal., 2019)

antioxidant study. TBARS and MDA are products of lipid peroxidation caused by oxidative stress (Kim, 2013). Decrease in TBARS and MDA levels indicated that there is reduction in the oxidative stress. As listed in Table 5, the extracts of *P. sarmentosum* were able to reduce TBARS and MDA *in vivo* and *in vitro* (Azlina et al., 2011; Mohd Zainudin et al., 2015; Wang et al., 2017). GPX and SOD are enzymes involved in the first line defense system against the reactive oxygen species in the body (ROS) (Kim, 2013). Antioxidant capability of products can be measured through the levels of these enzymes. GPX was reported to reduce hydroperoxide (H_2O_2) compounds to H_2O (Marín-García, 2014). SOD is the key to the regulation of ROS in the body by converting them into H_2O_2 where it will later be converted into water by the catalases (Younus, 2018). Based on Table 5, contradictory reaction between GPX and *P. sarmentosum* were obtained. Wang et al. (2017) reported an increased in GPX in piglets treated with *P. sarmentosum*. However, Azlina et al. (2011) reported a decline in GPX activity in rats treated with *P. sarmentosum*. No changes of SOD activity were observed in rats treated with methanolic extract of *P. sarmentosum* (Azlina et al., 2011). One study utilized *in vitro* MTT assay to evaluate the antioxidant activity of *P. sarmentosum* in H_2O_2 induced HUVEC (Ugusman et al., 2012). H_2O_2 is a reactive oxygen species that can cause mitochondrial disruption in cells (Spasic et al., 2013). MTT assay was commonly used in anticancer studies of compound through measure of cell cytotoxicity (Liu & Nair, 2018). In MTT, compounds were observed for its ability to reduce the MTT into formazan. Ugusman et al., (2012) found that aqueous extract of *P. sarmentosum* was able to improve the cell viability of H_2O_2 induced HUVEC. This showed that *P. sarmentosum* exhibit cytoprotective against oxidative cell damage.

ANTICANCER PROPERTIES OF P. SARMENTOSUM

Previous reports showed that *Piper* plants belong to one of the potential sources of drugs for cancer (Durant-Archibold et al., 2018; Wang et al., 2014). They were reported to possess cytotoxicity against cancerous and tumors cells. Approximately ten distinct Piper species have been reported to be used in traditional medicine to treat various types of cancer and cancer symptoms (Durant-Archibold et al., 2018). Compounds extracted from a variety of Piper species have been shown to be cytotoxic to a variety of malignant cell lines. Out of all the phytochemicals, amide alkaloid isolated from several *Piper* species was reported as one of the key components with anticancer activity (Durant-Archibold et al., 2018; Feng et al., 2019). Piplartine, an amide alkaloid, which was also observed to be present in *P. sarmentosum* and other *Piper* species, was one of the most prevalent compounds which showed strong anticancer properties against different carcinogens (Bokesch et al., 2011; Y. H. Wang et al., 2014).

Different plant extracts such as methanol, ethyl acetate, ethanol, hexane and protein extracts were used for the study on anticancer activity exhibited by *P. sarmentosum* (Bokesch et al., 2011; Ee et al., 2009; Sakilan et al., 2019). Ee et al., (2009) presented that different extract used resulted in different anticancer capability. Hexane extracts of *P. sarmentosum* were found to be more cytotoxic than ethyl acetate extracts against HeLa and MCF-7 human breast cancer cell lines (Ee et al., 2009). Another study by Sakilan et al. (2019) reported that the ethanolic extract of *P. sarmentosum* also shows moderate cytotoxicity against HeLa and MCF-7.

In vitro anticancer studies of *P. sarmentosum* that have been reported utilized different cancer cell lines such as HepG2, human invasive breast cancer cell line (MDA-MB-231), human colon cancer cell line (HT-29), renal clear cell carcinoma cell line (ccRCC), MCF-7, and nasopharyngeal carcinoma (HK-1) cell lines (Bokesch et al., 2011; Ee et al., 2009; Hematpoor et al., 2018; Hussain et al., 2020; Sakilan et al., 2019). Tetrazolium is the most used compound to test cell viability. As listed in Table 6, MTT assay was commonly used method to measure the cytotoxicity of *P. sarmentosum* against cancerous cell lines. MTT is a colorimetric assay that utilize biochemical marker compound to measure the metabolic activity of cells (Aslanturk, 2018). Change of MTT compounds into formazan indicates that cells are viable and have an active metabolism. *In vitro* MTT studied performed by Ee et al., (2009); Sakilan et al., (2019) stated that extracts of *P. sarmentosum* exhibit cytotoxicity against HeLa and MCF-7 cell lines with IC_{50} ranging from 9.8 µg/mL to 51.61 µg/mL and 14 µg/mL to 30.03 µg/mL. This indicates that extracts of *P. sarmentosum* possess moderate to strong anticancer activity.

Similar to what have been observed in the antioxidant studies, the anticancer properties exhibited by extracts of *P. sarmentosum* was due to the presence of its bioactive compounds (Ee et al., 2009; Hematpoor et al., 2018). The *Piper* species has been identified as a significant source of secondary metabolites capable of inducing apoptosis in cancer cells. Phenylpropanoids, asaricin, asarone and isoasarone purified from leaves of *P. sarmentosum* showed cytotoxicity against MDA-MB-231 (Hematpoor et al., 2018). Sakilan et al., (2019) noted the presence of potential anticancer compounds such as asarone and phytol. Protein compounds isolated from *P. sarmentosum* were shown to reduce the viability of HK-1 cell by more than 50% (Hussain et al., 2020), while the alkaloid langkamide and piplartine have been reported to exhibit promising anticancer activity (Bokesch et al., 2011). The summary on *in vitro* anticancer properties of *P. sarmentosum* is listed in Table 6.

Table 5: Summary of *in vitro* anticancer studies of *P. sarmentosum* (cont.).

No.	Experimental	Part	Solvent	Results	Reference
1.	*In vitro* MTT assays performed against HepG2 cell lines and non-malignant Chang's liver cell lines. Morphological changes ofcells observed.	Whole plants	Ethanol	Anticarcinogenic effect against HepG2 and non-malignant Chang's liver cell lines with IC_{50} values of 12.5 µg mL^{-1} and 30 µg mL^{-1}. Morphological changes observed.	(Zainal Ariffin et al., 2009)
2.	*In vitro* HIF-2 and XTT assays performed and testedagainst ccRCC cell line.	Roots, stems	Ethyl acetate	Compounds isolated from extracts showed inhibitory effect against HIF-2 with EC_{50} values from 5 to 60 µM.	(Bokesch et al., 2011)
3.	*In vitro* MTT assay performed on HeLa andMCF-7 cell lines. Alkaloids content of extracts were studied.	Aerial parts	Hexane, ethyl acetate	Hexane extract of *P. sarmentosum* showed better cytotoxicity against HeLa and MCF-7 cell lines comparedto ethyl acetate extract. Several alkaloid compounds were isolated and identified.	(Ee et al.,2009)
4.	*In vitro* MTT assay performed on HeLa, MCF-7 and HT-29 cancer cell lines. Phytochemical compositions were analyzed.	Leaves	Ethanol	Cytotoxic against HeLa, MCF-7and HT-29 with IC_{50} 51.61±23.03, 30.02±6.84 and 24.97±5.52 µg/mL respectively. Containsflavonoids, tannins, steroids, and alkaloids.	(Sakilan et al., 2019)
5.	*In vitro* MTT assay performed against normal non-malignant NP-69 and HK-1 cell lines	Plant proteins	Phosphate buffered saline	Protein extracts from *P. sarmentosum* showed no toxicity against normal NP-69 (>80% viability). Treatment with protein fraction from *P. sarmentosum* resulted in <50% cell viability of the HK-1.	(Hussain et al., 2020)

Conclusion

In conclusion, *P. sarmentosum* is a valuable source of herbal medicine. Different phytochemical compounds are present in all plant parts of *P. sarmentosum*. Different phytochemical analysis of *P. sarmentosum* identified the presence of different constituents including terpenoids, phenylpropanoids, flavonoids and alkaloids. It is concluded that *P. sarmentosum* possess antioxidant and anticancer effects. Next, it also showed *in vitro* and *in* vivo antioxidant activity where they were able to reduce serum MDA, TBARS, and increase GPX activity. *P. sarmentosum* showed anticancer efficacy in vivo against HepG2, HT-29, MCF-7, HeLa, MDA-MB-231, and HK-1 cancer cells. The presence of phytochemical compounds in *P. sarmentosum* contributes to both antioxidant and anticancer properties.

Conflict of Interest

There are no conflicts of interest.

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