Current Trends in Biotechnology and Pharmacy
Vol. 11 (4) 345-356 October 2017, ISSN 0973-8916 (Print), 2230-7303 (Online)

An updated review on Phytochemical and Pharmacological propeties of *Piper sarmentosum*

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Abstract

Piper sarmentosum is a well-known medicinal plant of Southeast Asia consist of many medicinal properties such as Anti-microbial, antifungal, antimalarial, antituberculosis, anti-mycobacterial, anticarcinogenic, antioxidant, anti-nociceptive, anti-inflammatory, antiamoebic, neuromuscular blocking activity, anti-obesity, antiangiogenesis, wound healing, cardiovascular activity, anti-hypertensive, antiulcer and Anticoccidial activity. It consists of adifferent class of compounds such as amide, phenylpropanoid, alkaloid, steroid, C- benzylateddihydroxyflavone, alkaloid amide, Phenylpropanoyl amides, and lignin. Therefore, current article reviews its phytochemical and pharmacological activities that will help for the future scientist.

Keywords:*Piper sarmentosum*; Phytochemistry; Pharmacology; alkaloid amide; Southeast Asia

Introduction:

Natural source is the vital part of basic human requirement especially in the field of health care (1). Plants are the essential foundation of medicine (2). It is used in different forms in different civilizations such as Ayurveda (3), traditional Chinese medicine (4), Unani herbalism, traditional Malaysian health care system (5), African herbal medicine (6) and many more. Piper *sarmentosum* Roxb belongs to family Piperaceae and is famous in the tropical and subtropical region (7). It is used in treatment of different kinds of ailments such as anti-microbial (8), anti-oxidant or oxidative stress (9-13), wound healing (14), anti-nociceptive, anti-inflammatory, anti-pyretic (15-16), osteoporosis (17), atherosclerotic (18), antimalarial (19), cardiovascular problems (20), antiangiogenesis (21-22), anti-hypertensive (23), antituberculosis (24), It is distributed in adifferent parts of Southeast Asia such as Malaysia, Indonesia, Thailand, Cambodia, Vietnam (25). Leaves and fruit of *Piper sarmentosum*can be seen in fig. 1.

Traditional uses : It has been known by different names in different parts of theworld. Leaves of *Piper sarmentosum* has been used traditionally as natural anti-oxidant. It is usually boiled in water and used to relieve fever in malaria and treating cough, flue, and rheumatism. It has been used as antifungal against foot's dermatitis. It has been known as food flavoring agents in Thailand (14). List of traditional uses along with common names is represented in table 1.

Bioactive compounds isolated from *Piper sarmentosum*: Bioactive compounds differ in different parts of the plant. Fruits of *Piper sarmentosum* possess adifferent class of compounds such as amides, lignan, piperic acid, steroidal class of compounds and phenyl alkane.

Fig. 1. (A) Leaves and (B) fruit of *Piper sarmentosum*(26)(27)

Table 1: Traditional medicinal uses

Plants parts	Common names	Traditional Medicinal uses	Reference
Leaves	Kadok, PokokKadok (Malaysia)	Natural antioxidant.In Malaysia, they are also eaten raw as ulam and the leaves are boiled in water and taken to relieve fever in malaria and treat coughs, flu, and rheumatism	(28)(29)
Roots, Leaves	Kudak (Malaysia) Sirihduduk, Akarbugu or Mengkadak (Indonesia)	The root is a remedy for tooth-ache and may be made into a wash for fungoid dermatitis on the feet. A decoction of the boiled leaves may be utilized to treat coughs, influenza, tooth-aches, and rheumatism	(19)
Leaves	Cha-plu, (Thailand)	Food flavoring agents and traditional medicines	(14)

Phenyl propanoids is the most common class of compounds found in leaves followed by alkaloid amide and piperamide. The aerial part of possessing C- benzylateddihydroflavones such as Sarmentosumins. List of bioactive compounds of *Piper sarmentosum* is represented in table 2. They are traditionally known as an antifungal agent. It is due to the prescene of alkaloid amides such as sarmentosine, sarmentine and brachyamide B (30)(34). Some of the benzene class of compounds inside *Piper sarmentosum* showed anti-microbial activity (31). The relationship among different pharmacological activities and their bioactive compounds have mentioned in table 3.

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Pharmacological activities: *Piper sarmentosum* possess different pharmacological activities. They were tested in vivo and in vitro test models. They contain different pharmacological activities in different parts of plants under different conditions. List of pharmacological activities was mentioned table 4.

Hypoglycemic activity: *Piper sarmentosum* possess hypoglycemic activity in animal models. The whole plant of was extracted with water macerated at 70°C and fractionated with methanol to give a soluble and insoluble portion. Male Wistar rats of 120-140 g were used. Diabetes was induced using streptozotocin.The hypoglycemic effect of the methanol soluble fraction of the water extract was found to be more active than water extract (39).

Anti-oxidant activity: Ethanolic extract of leaves and fruit of *Piper sarmentosum* possess in-vivo antioxidant activity. Oxidative stress was induced by CCl_4 in rats. It was administered orally for fourteen days. The level of hepatic function markers was observed and found effective. Fruits and leaves possess anti-oxidant activity (11). The methanolic leave extracts of *Piper sarmentosum* at 250 ug/ml were tested using Xanthine/Xanthine Oxidase (X/XOD) superoxide scavenging assay. It possesses high anti-oxidant activity (88%) as compared to superoxide dismutase standard (28).*Piper sarmentosum* is capable of reducing the oxidative stress in lungs by decreasing lipid peroxidation and maintaining the glutathione peroxidase activity towards the normal level. Leaves of *Piper sarmentosum* were macerated with absolute methanol and were tested thein-vivo model using male Wistar rats (10).

Anti-inflammatory activity: Methanolic extract of leaves of *Piper sarmentosum* leaves possesses anti-inflammatory activity while lacking antipyretic activity. It was extracted using cold extraction by macerating in 20 L of methanol for 7 days at room temperature (15). Leaves of *Piper sarmentosum* was extracted by soaking in distilled water and express anti-nociceptive activity, anti-inflammatory activity in a dose dependentmanner. Anti-inflammatory activity was performed by carrageenan-induced paw edema test whereas anti-nociceptive activity was performed by abdominal constriction and hot plate test (16).

Cardiovascular activity: Aqueous extract of *Piper sarmentosum* decreases atherosclerotic lesions in high cholesterolemic experimental rabbits. After treatment animals were sacrificed and aortic tissue was examined histologically (18). Furthermore, it was also effective to heal the integrity of diabetic cardiovascular tissues (left ventricular cardiac tissues and proximal aorta) examined under transmission electron microscope (20). It reduces oxidative stress damage, increases NO production and able to reduce blood pressure and cholesterol level (23).

Anti-microbial activity: *Piper sarmentosum* possess anti-fungal properties due to the presence of bioactive amide alkaloids. The crude extract was also active against methicilin-resistant *Staphylococcus aureus* (MRSA), *Escherichia coli*, *Vibrio cholera* and *Streptococcus pneumonia*. There are a number of bioactive compounds isolated from *Piper sarmentosum* that possesses anti-fungal activities as mentioned in table 3.

Miscellaneous activities: The leaves of aqueous plant extract of *Piper sarmentosum* was used for the healing of oral wounds (14). Fresh leaves of *Piper sarmentosum* was also effective to improve fracture healing which was assessed by the callus volume and callus scores (44).The methanol extracts of roots of appeared to be effective against caecalamoebiasis in female swiss albino mice (40). It induces anticarcinogenic activity through an intrinsic apoptosis pathway in HepG2 cells in vitro. Fresh plants were used in extraction, macerated under ethanolic extract (41). Leaves of methanolic extract of *Piper sarmentosum* possess a similar protective effect against stress-induced gastric lesions as omeprazole (46).

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Table 2: List of Bioactive compounds

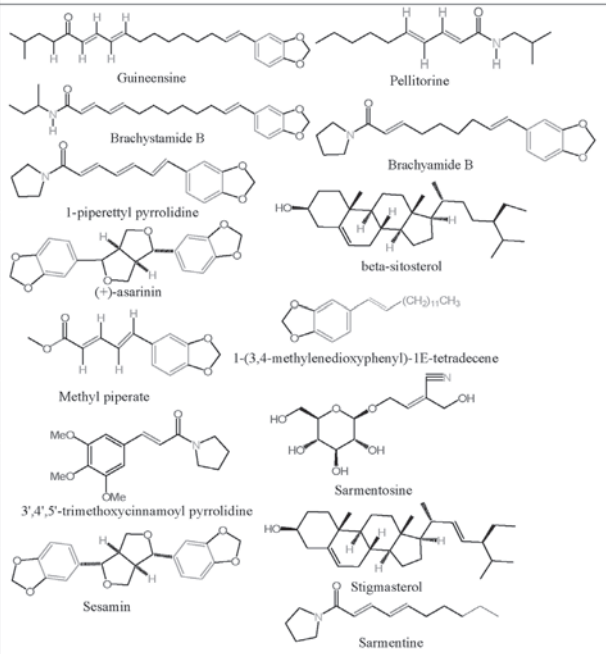
Name	Plant part	Class of compound	Structure	Reference
Pellitorine, guineensine, brachystamide B, brachyamide B, 1-piperettylpyrrolidine, 3',4',5'-trimethoxycinnamoylpyrrolidine	Fruits	Amide		(30)
(+)-asarinin, sesamin		Lignan		
β-sitosterol, stigmasterol		Steroidal class		
Methyl piperate		Piperic acid		
1-(3,4-methylenedioxyphenyl)-1E-tetradecene		Phenyl alkane		
Sarmentine, Sarmentosine		Amide		

Table 2: (Continue)

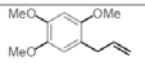
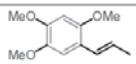
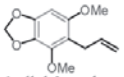
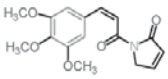
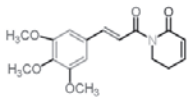
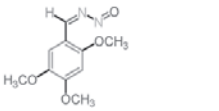
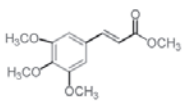
Name	Plant part	Class of compound	Structure	Reference
1-allyl-2,6-dimethoxy-3,4-methylenedioxybenzene; 1-allyl-2,4,5-trimethoxybenzene; 1-allyl-2-methoxy-4,5-methylenedioxybenzene; 1-(1-E-propenyl)-2,4,5-trimethoxybenzene	Leaves	Phenyl propanoid	   	(31)
1-nitrosoimino-2,4,5-trimethoxybenzene	Roots			(32)
Langkamide	Roots and stems	Alkaloid		(33)
Piplartine				
3,4,5-trimethoxycinnamic acid			 	

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Table 2: (Continue)

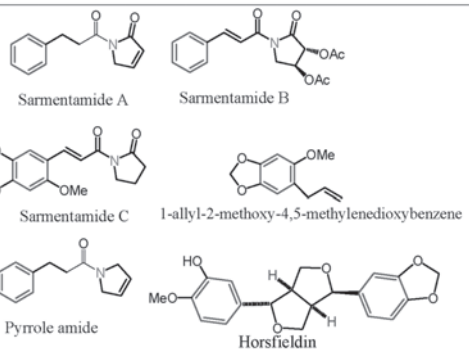
Name	Plant part	Class of compound	Structure	Reference`
Aromatic alkene	Roots			(34)
Sarmentamide A, Sarmentamide B, Sarmentamide C,		Amide		
Horsfieldin				
1-allyl-2-methoxy-4,5-methylenedioxybenzene				
pyrrole amide		Amide		

Table 2: (Continue)

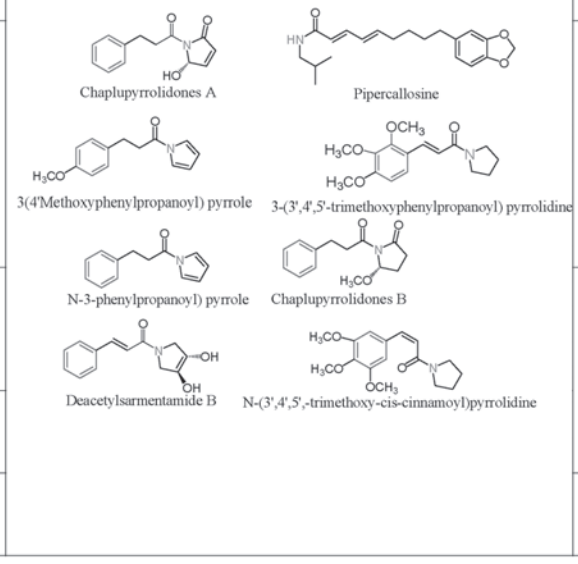
Name	Plant part	Class of compound	Structure	Reference
Chaplupyrrolidones A ChaplupyrrolidonesB Deacetylsarmentamide B	Leaves	Phenylpropanoyl amides		(35)
3-(3',4',5'-trimethoxyphenylpropanoyl) pyrrolidine N-3-phenylpropanoyl) pyrrole 3(4'Methoxyphenylpropanoyl) pyrrole	Aerial parts			(36)
Sarmentosumins A Sarmentosumins B Sarmentosumins C Sarmentosumins D	Aerial parts	C-benzylateddihydroflavones		(37)
Pipercallosine		Piperamide		
N-(3',4',5',-trimethoxy-cis-cinnamoyl)pyrrolidine	Leaves	Alkaloid amide		(38)

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Table 3: Compound reported with respect to pharmacological activities

Compound identified	Pharmacological activity	Reference
Sarmentine;sarmentosine	Antituberculosis and antiplasmodial activities	(30)(34)
Pellitorine;guineensine;brachyamide B,sarmentosine,1-(3,4-methylenedioxyphenyl)-1E-tetradecene	Antituberculosis activity	
1-allyl-2,6-dimethoxy-3,4-methylenedioxybenzene;1-allyl-2,4,5-trimethoxybenzene;1-allyl-2-methoxy-4,5-methylenedioxybenzene;1-(1-E-propenyl)-2,4,5-trimethoxybenzene	Anti-microbial activity	(31)
Sarmentosine,brachyamide B	Anti-fungal activity	(34)
N-[9-(3,4-methylenedioxyphenyl)-2E,4E,8E-nonatrienoyl]-Pyrrolidine;aromatic alkene	Anti-mycobacterial activity	
Langkamide; piplartine; 3,4,5-trimethoxycinnamic acid	Hypoxia Inducible Factor-2	(33)
Chaplupyrrolidones-B	α-glucosidase inhibitory activities	(35)
3-(3',4',5'-trimethoxyphenylpropanoyl) pyrrolidine; N-3-phenylpropanoyl) pyrrole; β-sitosterol	Anti-bacterial (gram-positive bacteria)	(36)

Table 4: Pharmacological activities reported

Pharmacological activity	Part used	Extract/Fraction/Isolate	Testing method; Experimental model	Animals/ Cell line culture	Dose	Results	Reference
Hypoglycemic effect	Whole plant	Macerated with Water at 70°C and methanol soluble and insoluble fraction	Diabetic induced in vivo via STZ-diabetes induction	Male Wistar rats	125mg/kg; 250mg/kg	The methanol soluble fraction of the water extract was found to be more potent than that of the water extract.	(39)
Anti-amoebic activity	Root	Macerated in absolute methanol	In-vivo model	Female Swiss albino mice	125, 250,500, 1000 mg/kg/day	The methanol extracts appeared to be effective against caecalamoebiasis in mice	(40)
Anticarcinogenic activity	Fresh plant material	Macerated in ethanolic extract	In-vitro	human hepatoma cell line (HepG2)	12.5 µg mL^{-1}	It inducesanticarcinogenic activity through an intrinsic apoptosis pathway in HepG2 cells in vitro	(41)
Anti-nociceptive and anti-inflammatory activities	Leaves	soaking (1:8; w/v) in distilled water for 72 h.	In-vivo model	Male Balb/c mice and Sprague–Dawley rats	30,100 and 300 mg/kg	It possessesanti-nociceptive and anti-inflammatory activities in a dose dependent manner	(16)
Anti-oxidant activity	Fruit and leaves	Ethanol extract	In-vivo model	Female Sprague–Dawley rats	250 and 500 mg/kg	Fruits and leaves possess anti-oxidant activity	(11)

Table 4: (Continue)

Pharmacological activity	Part use	Extract/Fraction /Isolate	Testing method; Experimental model	Animals/ Cell line culture	Dose	Results	Reference
Antioxidant activity	Leaves	Methanolic leave extracts	Xanthine/xanthine oxidase (X/XOD) superoxide scavenging assay	--	250µg/ml	Fractions of *Piper sarmentosum* consist of naringenin which is natural anti-oxidant	(28)
Neuromuscular blocking activity	Leaves	Macerated with methanol	In-vivo	Adult Wistar rat	3.2, 4.0, 4.8 and 6.4 mg/ml	*Piper sarmentosum* likely to inhibit neurotransmitter (acetylcholine) release at the presynaptic terminal	(42)
Atherosclerosis activity	Leaves	Aqueous extraction	In-vivo	Rabbit	62.5-500 mg/kg	*Piper sarmentosum* produce protective effect against atheroscleros	(18)
Antimalarial activity	Leaves	Chloroform and methanol	In-vitro	--	2.5 mg/ml	*Andrographispaniculata* also demonstrated higher antimalarial effect than *Piper sarmentosum*	(19)
Anti-obesity	Leaves	Decoction	In-vivo	Female Sprague–Dawley rats	1.25mg/kg	*Piper sarmentosum*water extract reduce the activity on 11-β-Hydroxysteroid dehydrogenase Type-1 Bioactivity	(43)

Table 4: (Continue)

Pharmacological activity	Part use	Extract/Fraction/Isolate	Testing method; Experimental model	Animals/ Cell line culture	Dose	Results	Reference
Antioxidant and antiatherosclerotic activities	Leaves	100 g of the powdered leaves in 900 ml of purified water and incubated in a high-speed mixer at 80°C for 3 hours.	In-vitro	--	150 µg/mL	The expressional suppression of ICAM-1 and Nox4 and induction of antioxidant enzymes might be an an important component of the vascular protective effect of *Piper sarmentosum*	(13)
Anti-tuberculosis activity	Leaves	Methanolic extract. Chloroform, ethyl acetate fractions of methanol. Combination of Isoniazid with different fractions	MIT in-vitro Assay	--	100µg/ml from the stock solution	Aqueous, ethanolic and Methanolic extract possess anti-TB activity with MIC 12.5 µg/ml, whereas chloroform and ethyl acetate possess 3.12 µg/ml. Concentration of Isoniazid (INH) was reduced to 75% when used in combination	(7)
	Root, stem, leaves and fruit	Aqueous and ethanolic extract					

Table 4: (Continue)

Pharmacological activity	Part use	Extract/Fraction/Isolate	Testing method; Experimental model	Animals/ Cell line culture	Dose	Results	Reference
Fracture healing	Fresh Leaves	Aqueous	In-vivo	Female Sprague-Dawleyrats	125 mg/kg	Improved fracture healing, as assessed by the reduced callus volumes and reduced callus scores.	(44)
Anti-inflammatory and antipyretic activities	Leaves	Extracted using cold extraction by macerating in 20 L of methanol for 7 days at room temperature.	In-vivo	Male Wistar rats	50, 100 and 200 mg/kg p.o	Methanolic extract of *P. sarmentosum* leaves possesses anti-inflammatory activity while lacking antipyretic activity	(15)
Antiangiogenesis Activity	Leaves	Petroleum ether, chloroform, methanol, n-hexane, chloroform, ethyl acetate fractions of methanol	In-vivo	Rat aorta model using adult Sprague-Dawley rats	100µg/ml	Chloroform extract and fraction have promising antiangiogenesis activity	(21)
Anti-microbial activity	Leaves	Extracted by percolation in 70% methanol	In-vitro	Disc Diffusion Test	100 mg/ml	*P. sarmentosum* has shown to have some antimicrobial properties against methicilin-resistant Staphylococcus aureus (MRSA).	(45)

Pharmacological activity	Part use	Extract/Fraction/Isolate	Testing method; Experimental model	Animals/ Cell line culture	Dose	Results	Reference
Oxidative stress	Leaves	Macerated in absolute methanol	In-vivo	Male Wistar rats	125 mg/kg body weight	*P. sarmentosum* is capable of reducing the oxidative stress in lungs by decreasing lipid peroxidation and maintaining the glutathione peroxidase activity towards the nomal level.	(10)
Cardiovascular activity	Leaves	Mixed with 1L of water and boiled for 1 hr	In-vivo	Sprague-Dawley Rats	0.125 g/kg	The results indicate that *P. sarmentosum* restores ultrastructural integrity in the diabetic cardiovascular tissues.	(20)
Wound Closure Activity	Leaves	Aqueous Plant extract	In-vitrocell proliferation assay	--	1 to 100 µg/mL	*P. sarmentosum*used for the healing of oral wounds	(14)
Antihypertensive agent	Leaves	An amount of 100 grams of dried leaves were added to 900 ml of distilled water and boiled at 80°C for three hours.	In-vivo	Wistar rats	Not more than 2 ml/ 100 g body weight	*P. sarmentosum* possess antioxidant activity thatreduces oxidative stress damage, increase NO production and able to reduce blood pressure and cholesterol level	(23)

Table 4: (Continue)

Pharmacological activity	Part use	Extract/Fraction/Isolate	Testing method; Experimental model	Animals/ Cell line culture	Dose	Results	Reference
Anti-Ulcer	Leaves	250 g leaves were mixed with 2.5 L of methanol	In-vivo	Male Wistar rats	500 mg/kg	*Piper sarmentosum* possesses a similar protective effect against stress-induced gastric lesions as omeprazole	(46)
Anticoccidial effect	stem leaves	Extracted using supercritical carbon dioxide	In-vivo	Wenchang broiler chicks	100-300 mg/kg of feed	It possessesanticoccidialproperties and beneficial effect on intestinal mucosa damage in broiler chickens that had been challenged by coccidiosis	(47)

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Conclusion:

Although a comprehensive literature available on *Piper sarmentosum* about its pharmacological properties and phytochemical potential but aclinical trial on identified compounds were not available yet. Furthermore, there is no identified compound of some pharmacological activities such as anti-cancer, anti-obesity, anti-ulcer, cardiovascular and wound healing activities. These pharmacological activities were may be due to thesynergistic effect of multiple bioactive compounds. There is still need of bioassay-guided fractionation of *Piper sarmentosum* on these pharmacological activities. Research on green technologies such as green solvents, new green extraction methods, and green processing technologies is yet to be evaluated.The use of silver nanoparticles as anantimicrobial agent is growing rapidly. *Piper sarmentosum* possesses anti-microbial activity. There is a significant scope of research in green synthesis of *Piper sarmentosum* silver nanomaterial.

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