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Review Article

Phytochemical and pharmacological activity of *Tiliacora triandra* (Colebr.) Diels

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Abstract

Tiliacora triandra (Colebr.) Diels is an indigenous plant in Southeast Asia belongs to the family of Menispermaceae. It has been widely used for cuisine and medicinal purposes since long time. Many studies have investigated and reported of its chemical constituents and pharmacological activities, however these data are scattered. Therefore, this article aims to review on its traditional uses, phytochemicals and pharmacological properties. Traditionally, this plant has been used for treatment of various diseases such as fever, diabetic, hypertension, and gastrointestinal diseases. Many alkaloids, phenolic compounds, fatty acids, and essential oils were found in different plant parts. Numerous pharmacological studies have been reported supporting those traditional uses such as antioxidant, neuroprotective, antidiabetic, antiplasmodial, antipyretic and anti-inflammatory, anticancer, and antimicrobial activities. Accordingly, this valuable plant seems to have a potential to develop as a functional food and new drugs in the future.

Keywords: *Tiliacora triandra*, Yanang, bioactive compounds, biological activity, leaves

1. Introduction

Tiliacora triandra (Colebr.) Diels is a climbing plant belongs to the family of Menispermaceae. It is commonly found in limestone hills, evergreen forest, and scrub jungle throughout Southeast Asia (Forman, 1991). In Thailand, it is known as “ya-nang”, or thao-ya-nang or thao-wan-khiao or choi-nang or yat-nang depending on the region of Thailand (Forest Herbarium). This plant has been utilized for culinary and medicinal purposes for a long time. The leaf is widely used as an ingredient in many Thai dishes such as bamboo shoot soup, spiced bamboo shoots, and senna leaf curry (Chaveerach *et al.*, 2016) and its juice is consumed as a functional beverage (Weerawatanakorn, Rojsuntornkitti, Pan, & Wongwaiwech, 2018). In addition, this plant has been generally used by folk healers for treatment of many diseases and as a constituent of traditional antipyretics in the national list of essential medicines of Thailand (National Drug System Development Committee [NDSDC], 2018). Numerous studies have been reported to evidence its health benefits and medicinal properties. However, to the best of our knowledge, these valuable data are scattered and there is no comprehensive review on this plant. Thus, the aim of this article is to review on traditional uses, phytochemicals and pharmacological properties of different parts of this plant.

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2. Botanical Data

Tiliacora triandra (Colebr.) Diels belongs to the Menispermaceae family. *Limacia triandra* (Colebr.) Hook. f. and *Cocculus triandrus* Colebr are botanical synonym of this plant (Forman, 1988). It is a climbing shrub whose stem is slender and has puberulous or glabrous. Leaves are elliptic or lanceolate about 6.5-11 cm long and 2-4 cm wide. It is a dioecious plant which means male and female flowers are on separate plant. Inflorescences are in axillary peduncle cymes with a few flowers. Male flowers are yellowish, small, and have 3 or 6 petals with 3 stamens. Female flowers are small, and have 6 petals. Fruits are drupe, obovoid 3-4 mm long, with branches (Forman, 1991). Roots are unstable, tortuous and conical in size. The root surface is grayish-yellow with longitudinal wrinkles and crossing with cracks (Singharachai, Palanuvej, Kiyohara, Yamada, & Ruangrungsi, 2011a).

3. Local and Traditional Uses

Tiliacora triandra is an indigenous plant in Southeast Asia and widely utilized in Thailand. The vine-stem is used as a cordage (Forman, 1991). The leaf is consumed as a vegetable and popular drunk as functional beverages (Weerawatanakorn *et al.*, 2018). It might be due to the raw leaves contain high levels of beta-carotene, vitamin A, calcium, and iron (Judprasong *et al.*, 2015).

Apart from culinary use, it has medicinal value in traditional and folk medicine. In Cambodia, the leafy shoot mixed with other plants are used for treatment of dysentery (Forman, 1991). In Thailand, the leaves and roots are used in the traditional antipyretic preparations (NDSDC, 2018). Moreover, it has been widely used by folk healers for treatment of many diseases. A decoction of the whole plant mixed with other plants is used for healing aphthous ulcer (Neamsuvan, Tuwaemaengae, Bensulong, Asae, & Mosamae, 2012). A decoction of the roots is used for lowering blood sugar (Neamsuvan, Madeebing, Mah, & Lateh, 2015), antipyretic and antidote (Maneenoon *et al.*, 2015), and treating gastrointestinal diseases such as GERD, constipation, diarrhea and bilharzia (Neamsuvan, Phumchareon, Bunphan, & Kaosaeng, 2016). In addition, a decoction of fresh roots and leaves is used for treatment of hypertension by drinking instead of plain water (Neamsuvan, Komonhiran, & Boonming, 2018).

4. Phytochemical Constituents

Various chemical constituents have been reported in the roots, stems and leaves of *T. triandra* as demonstrated in Figure 1. The roots and stems have many bisbenzylisoqui noline alkaloids, of which some have been reported in both parts including tiliacorine, tiliacorinine, nortiliacorinine A, tiliacorinine 2'-*N*-oxide and yanangcorinine (Dechatiwongse, Chavalittumrong, & Nutakul, 1987; Nutmakul *et al.*, 2016; Pachaly & Khosravian, 1988a; Pachaly, Tan, Khosravian, & Klein, 1986; Wiriyachitra & Phuriyakorn, 1981). Meanwhile yanangine, dinklacorine, (Pachaly & Tan, 1986a) tilianangine, (Pachaly & Tan, 1986b) tiliageine, protoquercitol, tilitriandrine, (Pachaly & Khosravian, 1988b) magnoflorine, nortiliacorine A, noryanangine, and norisoyanangine (Pachaly & Khosravian, 1988a) have been reported only in the stems. In addition, many fatty acids have been reported in the stem including 5,7-dihydroxy-6-oxoheptadecanoic acid, ethyl-5,7-dihydroxy-6-oxooctadecanoate, ethyl linolenate, ethyl linoleate, ethyl pheophorbide A, pheophorbide A (Makinde, Ovatlarnporn, Sontimuang, Herbette, & Olatunji, 2020), palmitic acid, dibenzylhydroxylamine, oleic acid and stearic acid (Makinde, Radenahmad, Adekoya, & Olatunji, 2020).

Phytochemical studies of the leaves have been intensively investigated in the past decade, and numerous bioactive compounds were explored. The alcoholic extracts showed the presence of tannins, triterpenes, flavonoids, saponins and alkaloids (Phadungkit, Somdee, & Kangsadalampai, 2012; Rattana, Phadungkit, & Cushnie, 2010). In addition, alkaloid oxoanolobine (Surapong, Benjamart, Ladachart, & Methin, 2016), and some polyphenols were identified such as santonin, minecoside, protopseudohypericin, 3-O-methylluteolin glucoside malonylated, monoepoxy-betacarotene, 3-demethoxy-9α-hydroxyligballinol-O-glucoside, p-hydroxybenzoic acid, flavone glycoside cinnamic acids derivative, and flavanone glycoside (Boonsong, Laohakunjit, & Kerdchoechuen, 2009). Quantification studies revealed high content of phenolic compounds, vitamin E, fatty acids, and essential oils. In 100 mg of the water extract contained quercetin 9,028.86 μg, cyanidin 307.22 μg, gallic acid 4.81 μg (Phunchago, Wattanathorn, & Chaisiwamongkol, 2015). The lyophilized leaves juice powder contained total chlorophyll 3,551.6 mg/kg, rutin 1,762.1 mg/kg, tannic acid 1,213.0 mg/kg, and isoquercetin 488.1 mg/kg, catechin 369.9 mg/kg, quercetin 62.6 mg/kg and gallic acid 42.4 mg/kg (Weerawatanakorn *et al.*, 2018). The GC-MS analysis of the methanolic extract revealed relatively high levels of vitamin E (26.29%), phytol (19.57%) and 1-cyclohexenylacetic acid (8.59%) and the other compounds such as oleamide, oleic acid, neophytadiene, palmitic acid, 5-hydroxymethyl-2-furancarboxaldehyde, and 2,6-dimethyl-3-(methoxymethyl)-benzoquinone (Chaveerach *et al.*, 2016). In addition, distillation of the fresh leaves yielded essential oil 0.544% and the GC-MS analysis revealed that the most abundant components were isophytol (35.27%), linoleic acid (15.71%), n-hexadecanoic acid (15.53%), and other compounds such as linalool, α-terpineol, p-vinylguaiacol, 1-hexanol, β-damascenone, neophytadiene, tetradecanoid acid, 3-hexen-1-ol, sphatulenol, benzeneacetal dehyde, and linalool oxide (Naibaho, Laohankunjit, & Kerdchoechuen, 2012).

5. Pharmacological Activity

5.1 Antioxidant activity

Reactive oxygen species and oxidative stress are found to be associated with pathogenesis of several diseases such as cancer, atherosclerosis, diabetes, arthritis, and neurodegenerative diseases. Many studies suggest evidence that antioxidants might have potential to prevent and ameliorate these diseases (Rajendran *et al.*, 2014). Several parts of *T. triandra* have been extensively investigated and reported for their antioxidant activities. Various *in vitro* assays were used for evaluation including radical scavenging of 1,1-diphenyl-2-picrylhydrazyl (DPPH) and 2,2-azinobis (3-ethylbenzothiazoline-6-sulfonic acid) diammonium salt (ABTS) cation, and nitric oxide, ferric reducing antioxidant power (FRAP), and determination of total phenolic compound (TPC) and total flavonoid compound (TFC).

According to the results shown in Table 1, *T. triandra* exhibited a wide range of antioxidant activities, which depended on various factors such as material, part used, solvent and extraction method. Even the same ethanolic roots extract was used, one study exhibited DPPH scavenging activity with IC_{50} value of 83.64 μg/ml (Singharachai, Palanuvej, Kiyohara, Yamada, & Ruangrungsi, 2011b), while in another study was 15.38 μg/ml (Juckmeta & Itharat, 2012). In addition, among different fractions of the twigs and leaves, the ethyl acetate soluble fraction of the twigs exhibited the highest activity for DPPH and FRAP assays, while the ethyl acetate soluble fraction of the leaves exhibited the highest activity for ABTS assay and the n-hexane soluble fraction of the twigs showed the best nitric oxide inhibition activity (Makinde, Ovatlarnporn, Adekoya, Nwabor, & Olatunji, 2019).

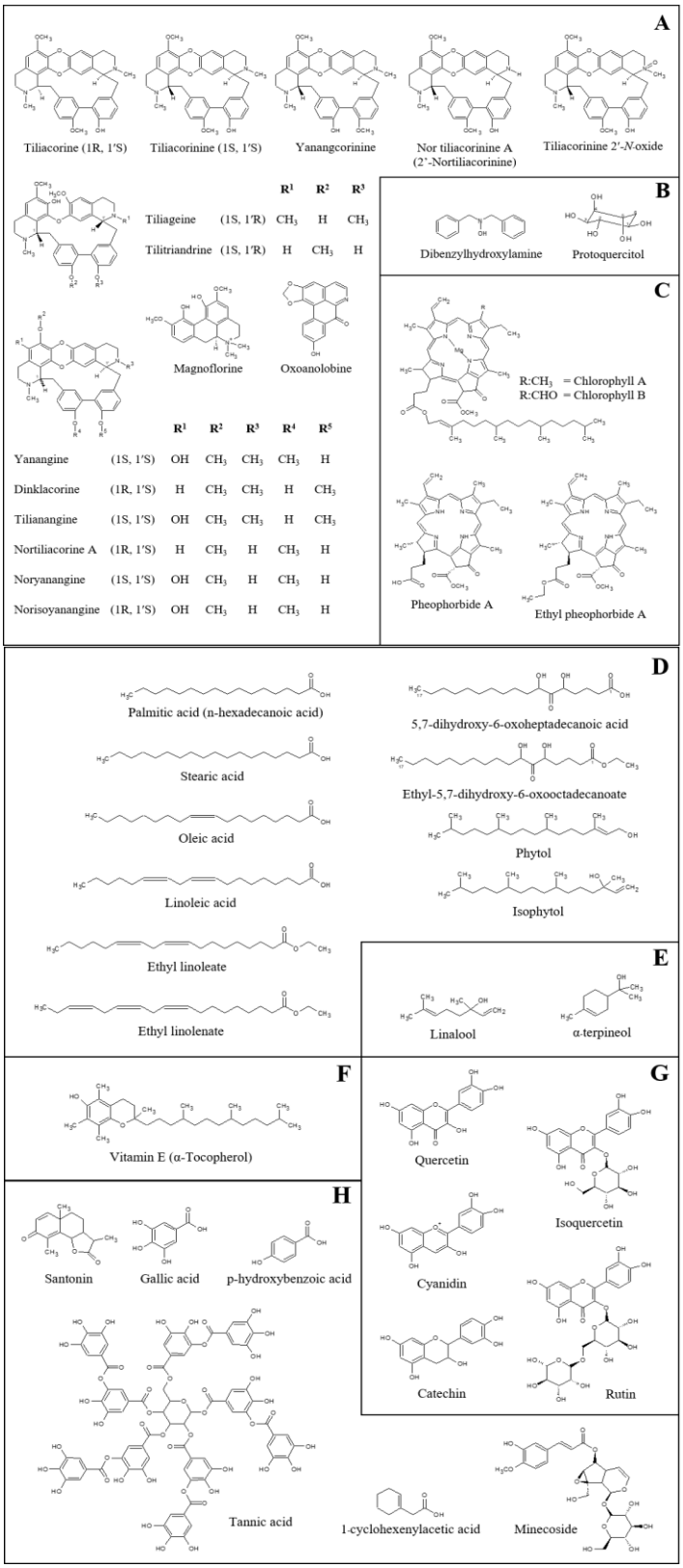

Figure 1. Chemical structures of some compounds identified in *Tiliacora triandra* (Colebr.) Diels. (A) alkaloids (B) miscellaneous (C) chlorophyll and its breakdown products (D) fatty acids (E) essential oils (F) vitamin E (G) flavonoids and (H) other phenolic compounds

Table 1. *In vitro* antioxidant activities, total phenolic content (TPC) and total flavonoid content (TFC) of different parts and extracts of *Tiliacora triandra* (Colebr.) Diels

Plant parts and extracts	DPPH assay (IC_{50})	ABTS assay (IC_{50})	FRAP assay Fe(II) equivalent	Other assays	References
Roots extracts					
Ethanol	83.64 μg/ml				Singharachai *et al.* (2011b)
Ethanol	15.38±0.25 μg/ml				Juckmeta *et al.* (2012)
Aerial extracts					
				Nitric Oxide assay (IC_{50})	
n-hexane fraction of twigs	2,436.83±22.49 μg/ml	190.04±8.59 μg/ml	402.21±13.62 μM/mg	30.50±0.47 μg/ml	Makinde *et al.* (2019)
Ethyl acetate fraction of twigs	424.16±2.69 μg/ml	21.62±0.03 μg/ml	1,116.54±3.9 μM/mg	87.51±8.72 μg/ml	
Ethyl acetate fraction of leaves	2,412.83±34.39 μg/ml	18.70 ± 3.68 μg/ml	276.59 ± 11.22 μM/mg	1,760.09±11.81 μg/ml	
Leaves extracts					
Ethanol	14.51±0.67 μg/ml				Phadungkit *et al.* (2012)
Methanol	8.4 mg/ml				Chaveerach *et al.* (2016)
				Total Flavonoid Content	
Petroleum ether	113.81±0.85 ppm		0.49±0.00 mmol/mg	7.22±0.08 mmolQE/mg	Rattana *et al.* (2010)
Dichloromethane	75.57±1.68 ppm		0.37±0.00 mmol/mg	17.04±0.06 mmolQE/mg	
Ethyl acetate	15.02±0.47 ppm		0.58±0.00 mmol/mg	14.71±0.08 mmolQE/mg	
Methanol	9.63±0.53 ppm		0.734±0.13 mmol/mg	18.68±0.28 mmolQE/mg	
Water	16.19±0.45 ppm		0.151±0.00 mmol/mg	2.01±0.07 mmolQE/mg	
80%Ethanol	6,346.05±1.17 μg extract/mg DPPH		0.27±0.02 mmol/g	22.63±1.53 mgCE/g	Nanasombat *et al.* (2019)
				Total Phenolic Content	
Water	0.197±0.018 mg/g	0.077±0.011 mg/g	0.054±0.002 mmol/g	101.25±1.81 mgGAE/g 97.899±1.735 mgGAE/g	Singthong *et al.* (2014)
Ethanol	0.333±0.024 mg/g	0.191±0.059 mg/g	0.034±0.001 mmol/g	26.703±1.642 mgGAE/g	
Acetone	0.419±0.091 mg/g	0.312±0.056 mg/g	0.014±0.001 mmol/g	16.456±2.968 mgGAE/g	
Ethanol (maceration)	0.1007±0.01 mg/ml			50.15±3.82 mgGAE/g	Soradech *et al.* (2018)
Ethanol (batch stirring at 30°C)	0.0968±0.01 mg/ml			58.02±4.11 mgGAE/g	
Ethanol (batch stirring at 40°C)	0.1131±0.01 mg/ml			59.13±4.81 mgGAE/g	
freeze-dried leaves juice	0.29±0.02 mgTE/g		0.34±0.03 mgGAE/g	0.94±0.04 mgGAE/g	Chuacharoen (2020)

IC_{50}=50% inhibitory concentration; DPPH=1,1-diphenyl-2-picryl hydrazyl; ABTS=2,2-Azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) diammonium salt; FRAP=Ferric Reducing Antioxidant Power; QE=Quercetin equivalent; CE=Catechin equivalent; GAE=Gallic acid equivalent; TE=Trolox equivalent

For the leaves extracts, the ethanolic extract exhibited DPPH scavenging activity with IC_{50} value of 14.51 μg/ml (Phadungkit *et al.*, 2012), while the methanolic extract was 8.4 mg/ml (Chaveerach *et al.*, 2016), the 80%ethanolic was 6,346.05 μg extract/mg DPPH (Nanasombat, Yansodthee &Jongjaited, 2019) and the freeze-dried leaves juice was 0.29 mg Trolox equivalent/g (Chuacharoen, 2020).

The different solvent extraction exhibited different antioxidant activity. Among petroleum ether, dichlorome thane, ethyl acetate, methanol and water, the methanolic extract displayed the best activity against DPPH and FRAP assays, and yielded the highest TFC (Rattana *et al.*, 2010). In another study, among water, ethanol and acetone, the water extract showed the highest radical scavenging of DPPH and ABTS, reducing power, and TPC (Singthong, Oonsivilai, Oonmetta-aree, & Ningsanond, 2014).

One study has been reported of the effect of different extraction method. Among maceration, and batch stirring extraction at 30°C and 40°C, the ethanolic extracted by batch stirring method at 30°C and 40°C yielded similar TPC. However, extraction at 30°C possessed the highest DPPH scavenging activity (Soradech, Kusolkumbot, & Thubthimthed, 2018).

5.2 Neuroprotective activity

Tiliacora triandra has been documented as an ingredient in Thai traditional rejuvenating and neurotonic remedies (Ingkaninan, Temkitthawon, Chuenchom, Yuyaem, & Thongnoi, 2003) and possessed antioxidant activity mentioned earlier. There are many studies reported on its neuroprotective activities (Table 2).

Table 2. Other pharmacological activities of *Tiliacora triandra* (Colebr.) Diels

Activity	Model used	Plant part	Extracts / compounds	Major findings	References
Neuroprotective	*In vitro*. AChE inhibition assay	Root	MeOH extract	42.29% inhibition at 0.1 mg/ml.	Ingkaninan *et al.* (2003)
		Leaf	80%EtOH extract	2.18% inhibition at 0.1 mg/ml.	Nanasombat *et al.* (2019)
	In vivo. Alcoholic rat	Aerial part	Water extract (100, 200, and 400 mg/kg, p.o.)	⇧memory deficit, ⇩AChE activity, ⇧neuron density, ⇩MDA level, and ⇧SOD, CAT, and GSH-Px activities.	Phunchago *et al.* (2015)
	In vivo. Cerebral ischemia/reperfusion mice	Leaf	EtOH extract (300 and 600 mg/kg, p.o.)	⇧spatial learning, ⇧spatial memory, ⇧learning flexibility and prevent hippocampal cell death.	Thong-asa *et al.* (2017)
				Pretreatment: ⇩calcium level and ⇩MDA level, ⇧GSH, SOD and CAT activities, attenuate brain infarction, and ⇩dead cells in the cerebral cortex and hippocampus.	Thong-asa and Bullangpoti (2020)
	In vivo. Male mice	Leaf	EtOH extract (300 and 600 mg/kg, p.o.)	⇧spatial learning, ⇧spatial memory, ⇧learning flexibility, ⇧choline acetyltransferase activity and ⇧hippocampal cell density.	Thong-asa and Laisangunngam (2018)
Antidiabetic	*In vitro.* α-amylase and α-glucosidase inhibition assays	Leaf	80%EtOH extract	78.28% α-amylase inhibition and 10.30%α-glucosidase inhibition at 1 mg/ml.	Nanasombat *et al.* (2019)
		Twig	n-hexane fraction	IC_{50}α-amylase=93.74 μg/ml. IC_{50}α-glucosidase=3.40 μg/ml.	Makinde *et al.* (2019)
		Aerial part	5,7-dihydroxy-6-oxoheptadecanoic acid	IC_{50}α-amylase=26.27 μM. IC_{50}α-glucosidase=11.58 μM.	Makinde, Ovatlarnporn *et al.* (2020)
	In vivo. STZ-induced diabetic rats	Leaf	EtOH extract (300 mg/kg, p.o. for 8 weeks)	⇩blood glucose level, ⇧serum insulin level, and activated the regeneration of pancreatic Islets of Langerhans.	Katisart and Rattana (2017)
	In vivo. Mice with high sugar intake	Leaf	EtOH extract (300 and 600 mg/kg, p.o.)	⇩blood glucose, ⇩serum insulin, and ⇧liver and muscle glycogen contents.	Thong-asa *et al.* (2019)
	In vivo. High-fat diet/ STZ induced diabetic rats	Aerial part	EtOH extract (100 and 400 mg/kg, p.o. for 30 days)	⇩blood glucose level, ⇩lipid profiles, and ⇧liver and kidney functions.	Makinde, Radenahmad, *et al.* (2020)
Antiplasmodial	*In vitro.* Clinical isolate *Plasmodium falciparum*	Root	MeOH extract and isolated compounds	MeOH extract: IC_{50}=17 μg/ml, Tiliacorinine: IC_{50}=3533±281 ng/ml, Tiliacorine: IC_{50}=675±96 ng/ml, Nor-tiliacorinine A: IC_{50}=558±41 ng/ml, alkaloid G: IC_{50}=344±44 ng/ml, alkaloid H: IC_{50}=916±122 ng/ml.	Pavanand *et al.* (1989)
	In vitro. P. falciparum CQ sensitive (3D7) and resistance (W2) strains	Stem, root	Different extracts and isolated compounds	The CH_2Cl_2 and MeOH extracts of the stem and root: IC_{50}=1.22 to 5.73 μg/ml against both strains of parasites. Tiliacorinine: IC_{50}W2=2.14μg/ml. Yanangcorinine: IC_{50}W2=1.55 μg/ml.	Nutmakul *et al.* (2016)
				Tiliacorinine and Yanangcorinine showed parasiticidal effect and potentiated the efficacy of CQ against CQ-resistant strain.	Nutmakul *et al.* (2020)
Antipyretic	*In vivo.* Yeast-induced fever rats	Root	Powder (40 mg/kg, p.o.)	Significantly reduced rectal temperature from the first hour after yeast injection.	Konsue *et al.* (2008)
Anti-inflammatory	*In vitro.* LPS induced NO production in RAW264.7	Root	EtOH extract	NO inhibitory activity: IC_{50}=54.65±5.34 μg/ml.	Juckmeta and Itharat (2012)
		Leaf	Lyophillized leaves juice	56% nitrite production inhibition at 500 μg/ml.	Weerawatanakorn *et al.* (2018)
	In vivo. Writhing test in mice	Leaf	Water extract (1 g/kg, p.o.)	55.7% inhibition of writhing reflex.	Tangsucharit *et al.* (2006)
Anticancer	*In vitro.* Various lung cancer cell lines	Root	EtOH extract	IC_{50}KB=42.1±4.5 μg/ml, IC_{50}Hep2= 45.2±7.1 μg/ml, IC_{50}A549=33.6±0.6 μg/ml, IC_{50}COR-L23=25.7±7.9 μg/ml, IC_{50}NCI-H226=19.5±1.4 μg/ml.	Juckmeta *et al.* (2019)

Table 2. Continued

Activity	Model used	Plant part	Extracts / compounds	Major findings	References
Anticancer	*In vitro.* Hepatoma cell line	Stem	EtOH extract	IC_{50}HepG2=81.06 μg/ml.	Lumlerdkij *et al.* (2020)
	In vitro. Colon cancer cell line	Leaf	MeOH extract	IC_{50}HT-29=203.52 μg/ml.	Manosroi *et al.* (2015)
	In vitro. Oral cavity cancer (KB) and lung cancer (NCI-H187) cell lines	Leaf	Different extracts	EtOAc extract: IC_{50}KB=15.81 μg/ml, IC_{50}NCI-H187=33.38 μg/ml. MeOH extract: IC_{50}KB=32.15 μg/ml, IC_{50}NCI-H187=11.93 μg/ml. Water extract: IC_{50}KB=12.06 μg/ml, IC_{50}NCI-H187=12.27 μg/ml. Oxonanolobine (isolated from MeOH extract): IC_{50}NCI-H187=27.6 μg/ml.	Surapong *et al.* (2016)
	In vitro. Sensitive (A549) and multidrug resistant (A549RT-eto) lung cancer cells	Leaf	Different extracts	CH_2Cl_2 extract: IC_{50}A549=22.0 μg/ml, IC_{50}A549RT-eto=48.5 μg/ml EtOH extract: IC_{50}A549=67.3 μg/ml, IC_{50}A549RT-eto=73.0 μg/ml.	Kaewpiboon *et al.* (2014)
	Human CCA *in vitro* and *in vivo*	Stem, root	Tiliacorinine	IC_{50}KKU-M055=4.5 μM, IC_{50} KKU-M213=5.7 μM, IC_{50}KKU-M214=6.1 μM, IC_{50}KKU-100=7.0 μM. Tiliacorinine rapidly reduced tumor growth in CCA xenografted mice.	Janeklang *et al.* (2014)
Antimicrobial	*In vitro.* Disc diffusion	Root	EtOH extract	The extract exhibited antibacterial and antifungal activities with the inhibition zone 6.8 to 16.3 mm.	Nuaeissara *et al.* (2011)
	In vitro. Broth microdilution	Aerial part	n-hexane and EtOAC fractions	The extracts exhibited antibacterial activity with MIC=0.39 to 6.25 mg/ml and MBC=1.5 to 12 mg/ml.	Makinde *et al.* (2019)
	In vitro. Disc diffusion and broth microdilution	Leaf	Essential oil	The essential oil exhibited antibacterial activity with the inhibition zone 10 to 16 mm, and MIC=6.25 μl/ml.	Naibaho *et al.* (2012)
	In vitro. Antimycobacterial activity	Root	Tiliacorine, Tiliacorinine, and 2′-nortiliacorinine	MIC=0.7 to 6.2 μg/ml against clinical isolates of multidrug-resistant *Mycobacterium tuberculosis.*	Sureram *et al.* (2012)

⇧=increase; ⇩=decrease; AChE=Acetylcholinesterase; MDA=malondialdehyde; SOD= Superoxide dismutase; CAT= Catalase; GSH-Px=Glutathione Peroxidase; STZ=Streptozotocin; CQ=chloroquine; LPS=lipopolysaccharide; NO=nitric oxide; CCA=Cholangiocarcinoma

Alzheimer's disease is a neurodegenerative disorder resulting in impaired memory and behavior. One of the most promising approaches is to enhance the acetylcholine level in the brain using acetylcholinesterase inhibitors. The methanolic root extract at 0.1 mg/ml inhibited 42.29% of acetyl cholinesterase activity (Ingkaninan *et al.*, 2003), while the 80%ethanolic extract of the leaves exhibited only 2.18% inhibition (Nanasombat *et al.*, 2019).

In animal studies, the extracts of *T. triandra* have been reported to improve brain dysfunction and possess neuroprotective, neurotonic and antioxidant activities. In alcoholic rat, the water extract of the aerial part at doses of 100, 200, and 400 mg/kg could improve memory deficit induced by alcohol consumption, suppress acetyl cholinesterase activity, increase neuron density in hippocampus, decrease malondialdehyde level, and increase the activities of antioxidant enzymes (Phunchago *et al.*, 2015). In cerebral ischemia/reperfusion (I/R) model, after 24 h surgery, the I/R mice were orally administered with the ethanolic leaves extract at doses of 300 and 600 mg/kg. The extracts could enhance spatial learning, learning flexibility, spatial memory and prevent hippocampal cell death (Thong-asa, Tumkiratiwong, Bullangpoti, Kongnirundonsuk, & Tilokskulchai, 2017). In addition, when the mice were administered with the extracts before I/R induction for 2 weeks, these extracts possessed neuroprotective effects by significantly reducing calcium and malondialdehyde levels, increasing the activities of antioxidant enzymes, attenuating brain infarction, and decreasing the percentage of dead cells in the cerebral cortex and hippocampus (Thong-asa & Bullangpoti, 2020). Moreover, these extracts possessed neurotonic effect by enhancing spatial learning, memory, and learning flexibility, and increasing choline acetyltransferase activity and hippocampal cell density in mice (Thong-asa & Laisangunngam, 2018).

5.3 Antidiabetic activity

Based on the folk knowledge, the roots (Neamsuvan *et al.*, 2015) and leaves (Udyanin, Bumrerraj, & Nimsuntron,

2013) has been used for reducing blood sugar. Several *in vitro* and *in vivo* antidiabetic studies, therefore, have reported supporting the folk knowledge (Table 2).

α-amylase and α-glucosidase inhibition assays were used for evaluation in *in vitro* studies. Inhibition of these enzymes resulted in delayed the glucose absorption in digestive tract and reduced the post-prandial hyperglycemia (Tundis, Loizzo, & Menichini, 2010). The 80%ethanolic extract of the leaves could inhibit the activity of both α-amylase (78.28%) and α-glucosidase (10.30%) (Nanasombat *et al.*, 2019). In another study, n-hexane soluble fraction of the twigs exhibited the inhibitory activities against α-amylase and α-glucosidase with the IC_{50} of 93.74 and 3.40 μg/mL, respectively (Makinde *et al.*, 2019). Six compounds, isolated from the aerial part, have been discovered and tested for the activity. Only 5,7-dihydroxy-6-oxoheptadecanoic acid possessed inhibitory activity against both α-glucosidase (IC_{50}=11.58 μM) and α-amylase (IC_{50}=26.27 μM), while the rest could inhibit only α-glucosidase with IC_{50} values ranging from 22.11 to 424.06 μM (Makinde, Ovatlarnporn, *et al.*, 2020).

In *in vivo* studies, after administration of the ethanolic leaves extract (300 mg/kg) for 8 weeks, the extract significantly decreased blood glucose level, increased serum insulin level, and activated the regeneration of pancreatic Islets of Langerhans in diabetic rats (Katisart & Rattana, 2017). In another study, the ethanolic leaves extract (300 and 600 mg/kg) significantly decreased the blood glucose and serum insulin, and increased the liver and muscle glycogen contents in mice with high sugar intake (Thong-asa, Prasertsuksri, Sakamula, & Nimnuan, 2019). Furthermore, the ethanolic extract of the aerial part significantly reduced blood glucose level, lipid profiles (except HDL-cholesterol), and improved liver and kidney functions in high fat diet and streptozotocin-induced diabetes in rats (Makinde, Radenahmad, *et al.*, 2020).

5.4 Antiplasmodial activity

Malaria is still a global health problem, caused by *Plasmodium* species. Especially, *P. falciparum* is the most virulent strain and could develop resistance to almost all available drugs (Nutmakul *et al.*, 2016). These stimulate efforts to continuously discover new antimalarials. In countries where malaria is endemic, such Thailand, numerous plants used to treat malaria have been investigated including *T. triandra* roots which is used as antipyretics and prescribed in antimalarial preparations in folk medicine (Dechatiwongse *et al.*, 1987).

As shown in the Table 2, the methanolic roots extract inhibited clinical isolate *P. falciparum* with IC_{50} of 17 μg/ml. Five bisbenzylisoquinoline alkaloids, tiliacorinine, tiliacorine, nor-tiliacorinine A, alkaloid G, and alkaloid H were further isolated and exhibited the IC_{50} values ranging from 344 to 3533 ng/ml (Pavanand, Webster, Yongvanitchit, & Dechatiwongse, 1989). In another study, the stems and roots extracts were tested against *P. falciparum* chloroquine-sensitive (3D7) and chloroquine-resistant (W2) strains. The chloroform extracts and methanolic extracts of both parts exhibited potent activity against both parasite strains with IC_{50} values ranging from 1.22 to 5.73 μg/ml. Tiliacorinine and yanangcorinine were further bioassay-guided isolated and exhibited the activity against W2 strain with IC_{50} values of 2.14 and 1.55 μg/ml, respectively (Nutmakul *et al.*, 2016). In addition, these compounds showed parasiticidal effect with a slow onset of action and could potentiate the efficacy of chloroquine against chloroquine-resistant strain since their structures contain many aromatic rings and a protonated nitrogen which is a specific structure for chloroquine resistance reversal agents (Nutmakul *et al.*, 2020).

5.5 Antipyretic and anti-inflammatory activities

In Thailand, the root of *T. triandra* is used for treatment of fever and the leaf juice is used for decreasing body temperature by folk healer (Maneenoon *et al.*, 2015). In the same way, the roots and leaves are used in traditional antipyretics listed in the national list of essential medicines namely, "ha-rak" or "bencha-loga-wichian" (BLW), and "mahanin-taengtong" preparations (NDSDC, 2018). Especially, BLW has been widely used and confirmed its healing property by scientific approach. In yeast-induced fever rats, oral administration of BLW powder significantly reduced rectal temperature and the best activity was observed in *T. triandra* powder (Konsue, Sattayasai, Puapairoj, & Picheansoonthon, 2008). In addition, the ethanolic extracts of BLW and *T. triandra* showed nitric oxide inhibitory activity on LPS-induced RAW 264.7 cell lines with IC_{50} values of 40.36 and 54.65 μg/ml, respectively (Juckmeta & Itharat, 2012).

In addition, the lyophillized leaves juice (500 μg/ml) inhibited 56% nitrite production in LPS-induced RAW 264.7 cell lines by down-regulation of iNOS and COX-2 expression (Weerawatanakorn *et al.*, 2018). In another study, oral administration of the water leaves extract (1 g/kg) inhibited writhing reflex by 55.7% in acetic acid-induced writhing model in mice (Tangsucharit, Kukongviriyapan, Kukongviriyapan, & Airarat, 2006). The antipyretic and anti-inflammatory activities of *T. triandra* extract from the roots and leaves are summarized in Table 2.

5.6 Anticancer activity

Tiliacora triandra is one of the plants that frequency used by folk healer in anticancer formulation (Manosroi *et al.*, 2015) and cancer prevention (Lumlerdkij, Boonrak, Boorana subkajorn, Akarasereenont, & Heinrich, 2020). Several parts of this plant has been investigated and reported for anticancer activity against various cancer cell lines (Table 2).

The ethanolic root extract exhibited cytotoxicity on several lung cancer cell lines including KB, Hep2, A549, COR-L23, and NCI-H226 with the IC_{50} values ranging from 19.5 to 45.2 μg/ml (Juckmeta *et al.*, 2019). The ethanolic stem extract possessed cytotoxicity on HepG2 cell line with IC_{50} of 81.06 μg/ml (Lumlerdkij *et al.*, 2020). The methanolic leaves extract showed cytotoxicity against human colon cancer cell line (HT-29) with IC_{50} value of 203.52 μg/ml (Manosroi *et al.*, 2015). In another study, the ethyl acetate, methanolic and water extracts exhibited cytotoxicity against oral cavity cancer (KB) and lung cancer (NCI-H187) cell lines with IC_{50} values ranging from 11.93 to 32.15 μg/ml, and oxonanolobine, a main active compound isolated from the methanolic extract,

possessed the activity against NCI-H187 with IC_{50} of 27.6 μg/ml (Surapong *et al.*, 2016).

Moreover, different extracts of the leaves were tested against sensitive (A549) and multidrug resistant (A549RT-eto) lung cancer cells. The dichloromethane extract exhibited the most cytotoxic effect against both sensitive and resistant cells with IC_{50} of 22.0 and 48.5 μg/ml, respectively. However, although the hexane extract was inactive, a mixture of fatty acids isolated from the hexane extract possessed a multidrug resistance reversing activity by enhancing P-glycoprotein function in A549RT-eto cell line (Kaewpiboon, Winayanuwattikun, Yongvanich, Phuwapraisirisan, & Assavalapsakul, 2014).

Tiliacorinine, an alkaloid isolated from the roots and stems, displayed antiproliferative effect on cholangiocarcinoma cell lines and antitumor activity in animal model. It inhibited growth of four human cholangiocarcinoma cell lines with IC_{50} values ranging from 4.5-7.0 μM by inducing apoptosis via caspase-activation pathways and rapidly reduced tumor growth in cholangiocarcinoma xenografted mice (Janeklang *et al.*, 2014).

5.7 Antimicrobial activity

The ethanolic roots extract exhibited wide spectrum antimicrobial activity against Gram positive bacteria (*Stahylococcus aureus*, methicillin-resistant *S. aureus*, and *Streptococcus pyrogenes*), Gram negative bacteria (*Escherichia coli*, *Shigella spp*, *Salmonella typhimurium*, *Acinetobacter buamannii*, and *Bacillus subtilis*) and *Candida albicans* with the inhibition zone ranging from 6.8 to 16.3 mm (Nuaeissara, Kondo, & Itharat, 2011). In another study, the n-hexane and ethyl acetate fractions of the aerial part exhibited the activity against *B. cereus*, *E. coli*, *S. aureus*, and *Listeria monocytogenes* with the MBC values ranging from 1.5 to 12 mg/ml (Makinde *et al.*, 2019). The essential oil extracted from the leaves possessed the activity against *S. aureus*, *B. cereus*, *E. coli*, and *Salmonella spp.* with inhibition zone of 16, 14, 13 and 10 mm, respectively and the MIC values of 6.25 μl/ml. (Naibaho *et al.*, 2012). Moreover, Tiliacorinine, 2'-nortiliacorinine, and tiliacorine, isolated from the roots, were tested against 59 clinical isolates of multidrug-resistant *Mycobacterium tuberculosis* and exhibited the MIC values ranging from 0.7 to 6.2 μg/ml. (Sureram *et al.*, 2012). The antimicrobial activity of this plant is summarized in Table 2.

5.8 Other activities

The ethanolic leaves extract (30 mg/plate) inhibited mutagenicity of nitrite treated 1-aminopyrene on *S. typhimurium* TA 98 and TA 100 by 44.84% and 58.84%, respectively (Phadungkit *et al.*, 2012). In another study, the ethanolic and water extracts of the roots at concentrations of 5-15 mg/ml showed strong mutagenic inhibition ranging from 88.42 to 123.12%. These extracts did not exhibit directly mutagenic towards on both strains but exhibited indirect mutagenicity induced by nitrosation (Singharachai *et al.*, 2011b).

Since BLW has long been used for treatment of fever and skin rash, BLW and its constituent plants were investigated for anti-allergic activity. The ethanolic extract of BLW showed inhibitory effect on the release of β-hexosaminidase from RBL-2H3 cells with IC_{50} value of 39.8 μg/ml, whereas *T. triandra* was inactive (IC_{50}>100 μg/ml) (Juckmeta, Thongdeeying, & Itharat, 2014).

In anti-grey hair activity, the ethanolic leaves extract not only possessed antioxidant activity, it stimulated tyrosinase activity with SC_{50} values ranging from 3.46 to 3.97 mg/ml without cytotoxicity to human dermal skin fibroblast and melanoma (B16F10) cells. In addition, at concentration of 0.05–1.0 mg/ml, the extract exhibited the potential of stimulating melanin ranging from 128.69 to 131.46% (Soradech *et al.*, 2018).

6. Toxicity

Based on the folk and traditional knowledge, the root and aerial parts of *T. triandra* are often prepared by boiling with water and no side effects reported. Several toxicity studies are scientific evidence supporting this knowledge. The water extract of the whole plant did not produce acute or subchronic toxicity in rat, in terms of mortality, changes in internal organ weight, gross appearance and histopathology of internal organs, hematological profiles, and animal behaviors (Sireeratawong *et al.*, 2008). In another studies, the water extract of the stems and roots did not exhibit cytotoxicity on peripheral blood mononuclear cells (IC_{50}>100 μg/ml) while the dichloromethane and methanolic extracts exhibited cytotoxicity with IC_{50} values ranging from 8.17 to 26.26 μg/ml (Nutmakul *et al.*, 2016). In the same way, the water extract of the roots was less toxic on *Artemia salina* than the ethanolic extract with LC_{50} values of 200 and 44 μg/ml, respectively (Singharachai *et al.*, 2011b).

7. Future perspectives

The aerial and root parts of ***T. triandra*** have been used as a culinary ingredient and a medicinal plant for a long time without any side effect reported**.** The aerial part, especially leaves, contain rich of nutrients and many phytochemicals such as flavonoids and other phenolic compounds**.** In addition, it has been reported to have antioxidant, neuroprotective, antidiabetic, anti-inflammatory, and anticancer activities**.** From a commercial perspective, the aerial part of this plant should be further studied in details for development as functional foods or nutraceuticals. For the root part, it is generally used in traditional medicine to treat fever including malaria fever and has scientific studies supporting the traditional uses. Moreover, the root extracts and its bisbenzylisoquinoline alkaloids possessed anti microbial and anticancer activities which should be further studied on mechanisms of action and efficacy in human in order to develop as new drugs.

8. Conclusions

Tiliacora triandra (Colebr.) Diels is an indigenous plant in Southeast Asia which has been long time used for cuisine and medicinal purposes. Numerous studies have been investigated and reported particularly in Thailand. However, these interesting data are scattered. This article is the first review of the traditional uses, phytochemicals and pharmacological properties of this plant. Apart from high nutritional value, many ethnomedicinal survey studies

revealed its medicinal properties for treatment of several diseases such as fever, diabetic, hypertension, and gastrointestinal diseases. These properties might be attributed to the presence of a variety of bioactive compounds such as bisbenzylisoquinoline alkaloids, flavonoids, phenolic compounds, fatty acids, and essential oils which have been found in different parts of this plant. Various pharmacological activities such as antioxidant, neuroprotective, antidiabetic, antiplasmodial, antipyretic and anti-inflammatory, anticancer, and antimicrobial activities, have been reported as evidence supporting the traditional uses. In addition, based on the history of consumption and use in medicinal remedies without any reported side effect and proving by several toxicity studies, this valuable plant seems to be safe and has potential to develop as functional foods and new drugs in the future. However, further studies on mechanisms of action and efficacy in human are still needed to be explored.

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