Phytochemicals and Biological Activity of *Tetracera scandens* Linn. Merr. (Dilleniaceae): A Short Review

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Tetracera scandens is a southeast Asian shrub that belongs to family Dilleniaceae. Over the years, different parts of the plant have been used for the management of different diseases, including diabetes mellitus, hypertension, rheumatism, diarrhea, hepatitis, and inflammation. This variety of medical indications has attracted the attention of many researchers to this plant species, leading to the conduction of many research studies on different parts of the plant. These studies have confirmed some of the aforementioned activities of the plant, whereas other indications remain to be ascertained. This article is an attempt to summarize the studies conducted on *T. scandens* and to explore the isolated phytochemicals.

**Keywords:** Diabetes mellitus, hypertension, phytochemicals, *Tetracera scandens*

**Introduction**

*Tetracera scandens* Linn. Merr. is a medicinal plant that belongs to family Dilleniaceae. It is native to Malaysia, Vietnam, Indonesia, Philippines, India, Southern China, Thailand, and other Southeast Asian countries. It is usually found in tropical thickets and forest margins. *T. scandens* has many synonyms including *Tetracera sarmentosa*, *Tragia scandens* L., *Delima sarmentosa* L., *Tetracera hebecarpa* (DC.) Boerl, *Delima hebecarpa* DC, and *Tetracera monocarpa* Blanco. Similarly, it has numerous local names, with the most common is the English name, stone leaf. In Malaysia, it is usually called Mempelas, Akar Mempelas, Mempelas Kasar, Mempelas Putih, Pampan, or Palas.[1,2] Furthermore, *T. scandens* is locally known as Akosempalay in Indonesia,[3] as Malakatmon in the Philippines,[4] and as Day Chieu in Vietnam.[5]

*T. scandens* is an evergreen shrub that grows to 2 m in height. In thickets, the plant usually grows as a woody climber, reaching up to 30 m. It has simple, petiolate leaves that are arranged in opposite pairs along the stem. Moreover, the leaf blade is characterized by its ovate shape, leathery and scabrous texture, serrated margin, and acute apex [Figure 1]. The new leaves are reddish-pink in color before turning green upon maturation.[6]

**Ethnobotanical Uses**

Due to their rough texture, the dried leaves of *T. scandens* are used as sandpaper by local handicrafts for wood-based objects. Sometimes, the young plant stems are used as ropes due to their flexibility and toughness.[7] Moreover, different parts of the plant have been used as folk medicines for the management of a wide range of diseases. Interestingly, different populations have used the same part of *T. scandens* for different indications. In the Philippines, an infusion of the stem of *T. scandens* is administered internally for management of hemoptysis in tuberculosis and applied externally to soothe sore throat, due to its high content of tannins. However, Malaysians take the decoction of plant stem orally to overcome the weakness accompanying fever and influenza.[8] Moreover, they administer a decoction of the whole plant after childbirth as a tonic. Young shoots are usually crushed into fine powder, then applied topically in the form of a poultice to treat snake bites in Indonesia.[6] In Vietnam,
stem and leaves are used for management of hepatitis, rheumatism, gout, inflammation, and back pain.\[^8\] Furthermore, the pulverized leaves are dispersed in water and administered for treatment of diarrhea, or boiled with water (i.e., decoction) and applied externally to boils. The root of \textit{T. scandens} has also been used for management of diarrhea, in addition to its use in burn mixtures. The stem’s sap has been administered orally as an antitussive, whereas stem’s infusion has been used as a gargle for treatment of oral candidiasis. The roots are ground and their juice is applied to mouth ulcer.\[^9\] The plant has also been used traditionally for the treatment of diabetes mellitus (DM), hypertension, fever, urinary disorders, internal pains and edema.\[^2,8\] Despite the wide range of traditional uses, only a few indications are supported with scientific evidences. Hence, more efforts are still needed to investigate the unexplored potential of \textit{T. scandens}. The scientifically justified uses will be discussed briefly in the following paragraphs with making highlights on the isolated bioactive compounds.\[^9\] Lima \textit{et al.}\[^{10}\] reported that flavonoids and terpenoids constitute the major bioactive constituents amongst plants of family Dilleniaceae. The findings of the following studies are in full agreement with those obtained by Lima \textit{et al.}\[^{10}\] as most of the isolated compounds belong to these two classes.\[^9\]

**Medicinal Activities of \textit{Tetracera scandens}\[^{2,8}\]**

**Antidiabetic activity**

Lee \textit{et al.}\[^{5}\] were the first to investigate the antidiabetic potential of \textit{T. scandens} and tried to isolate the phytoconstituents responsible for its antihyperglycemic properties. A series of fractionations and purifications of the methanol extract of a branch of \textit{T. scandens} using various chromatographic techniques led eventually to the isolation of five isoflavones with previously known structures. The isolated flavonoids include genistein, 3’5’-diprenylgenistein, 6, 8-diphenylgenistein, derrone, and alpinumisoflavone.\[^{5}\]

Glucose-uptake stimulant effect was assessed for each of the isolated metabolites. Genistein did not enhance glucose-uptake at all tested concentrations, whereas the other four compounds produced a considerable increase in the basal and insulin-treated glucose uptake. Furthermore, muscle cell toxicity was investigated for each compound. Compounds 3-5 did not show any toxic effect at concentrations up to 60 µM after a 24-h treatment. On the contrary, genistein and 3’5’-diprenylgenistein showed muscle cell toxicity with half-maximal inhibitory concentration (IC\(_{50}\)) values of 34.27 and 18.69 µM, respectively. Results of this study confirmed the antihyperglycemic effect of \textit{T. scandens}. Moreover, compounds 3–5 were considered the probable lead candidates for antidiabetic drug development without exerting toxicity to muscle cells.\[^{5}\]

Another study by Umar \textit{et al.}\[^{2}\] aimed to evaluate the antidiabetic effect of \textit{T. scandens} leaf extracts \textit{in vivo}. Firstly, a separate experiment was performed on normal healthy male rats to investigate the toxicity of both aqueous and methanol extracts of the leaves at different concentrations. No mortality or behavioral changes were observed in the extracts-treated animals, suggesting the safety of both aqueous and methanol extracts. After the confirmation of safety, the main experiment was carried out in order to investigate the effectiveness of \textit{T. scandens} leaves as an antidiabetic herb. Healthy and alloxan-induced diabetic rats were fed orally with aqueous and methanol extracts of \textit{T. scandens} leaves,
and blood glucose levels were measured every 2 h (at 0, 2, 4, 6, and 8 h). The results were compared with those of a positive control group treated with the antidiabetic drug glibenclamide at a concentration of 0.25 mg/kg of body weight. Both aqueous and methanol extracts produced a significant fall in the fasting blood glucose levels of diabetic rats (as compared to glibenclamide) without inducing hypoglycemia in healthy nondiabetic rats. Moreover, the aqueous extract showed a more potent antihyperglycemic effect than the methanol extract.\(^2\)

Furthermore, the total contents of phenols and flavonoids were measured spectrophotometrically in both aqueous and methanol extracts and were expressed as gallic acid equivalents (GAE) and quercetin equivalents (QE) mg/g of plant extract, respectively. The chemical characterization of the aqueous extract resulted in 4.75 GAE mg/g of phenolic compounds and 5.77 QE mg/g of flavonoids, whereas the methanol extract was found to contain 7.26 GAE mg/g of phenolic compounds and 6.34 QE mg/g of flavonoids.\(^2\)

Phytochemical investigation of the methanol extract of *T. scandens* leaves has resulted in the identification of three terpenoids and six flavonoids. The terpenoids were found to be stigmasterol, betulinic acid, and an isomeric mixture of sitosterol (\(\Delta^2\)) glycoside and stigmasterol (\(\Delta^{5,22}\)) glycoside, whereas the flavonoids were quercetin, hypolectin, isoscutellarein astragalin, kaempferol, and kaempferol-3-O-(6‴-O-p-trans-coumaroyl) glucoside. Further assay of hypolectin showed its adipocyte stimulation and skeletal muscle glucose-uptake stimulation activities, suggesting its usefulness for the management of type 2 DM.\(^{11}\)

**Xanthine oxidase inhibitory activity**

Nguyen *et al.*\(^{12}\) reported xanthine oxidase (XO) inhibitory activity of the 1:1 methanol:water extract of *T. scandens*, with an IC\(_{50}\) value of 15.6 µg/mL. Nguyen and Nguyen\(^{13}\) followed the activity-guided fractionation approach to characterize the metabolites responsible for XO inhibitory activity. Quercetin (IC\(_{50}\) = 1.9 µM), kaempferol (IC\(_{50}\) = 4 µM), tiliroside (13) (IC\(_{50}\) = 10.7 µM), betulinic acid (IC\(_{50}\) = 20.8 µM), platanic acid (IC\(_{50}\) = 42.3 µM), and emodin (IC\(_{50}\) >100 µM) were isolated from the methanol extract of *T. scandens*’ stem. In addition to these previously known flavonoids, a new nor-lupane triterpene was also isolated. The triterpene was found to be 28-O-β-D-glucopyranosyl ester of platanic acid (with IC\(_{50}\) of 65.9 µM). It is noteworthy that quercetin was the most potent of the isolated compounds with IC\(_{50}\) of 1.9 µM, even more potent than the prototype XO inhibitor allopurinol (IC\(_{50}\) = 2.5 µM).

**Antioxidant and hepatoprotective activity**

The leaves of *T. scandens* have been traditionally used in folk medicine for the treatment of hepatitis. Thanh *et al.*\(^{14}\) proposed that the hepatoprotective effect of *T. scandens* is due to the antioxidant properties of the plant metabolites. To explore the hepatoprotective potential of *T. scandens* and to prove their hypothesis, Thanh *et al.*\(^{15}\) conducted an *in vivo* study using a model of acute hepatitis based on the well-known hepatotoxin “carbon tetrachloride” (CCL\(_4\)). Metabolism of CCL\(_4\) results in the production of reactive oxygen species (ROS), including trichloromethyl free radical (CCL\(_4\)^{'}) and trichloromethyl peroxy radical (CCL\(_4\)OO'). Hepatotoxicity caused by CCL\(_4\) is mediated by the induction of oxidative stress in the hepatic tissue, leading eventually to hepatic necrosis and fibrosis.

Animals were divided into three groups each of 10 rats. In one group, no pretreatment was performed (control group). In the second group, a single intraperitoneal injection of the hepatotoxin CCL\(_4\) was performed (CCL\(_4\)-treated group). In the last group, rats were pretreated with a once-daily dose of the ethanol extract of *T. scandens* leaves (orally as aqueous suspension) for seven consecutive days. After that, all animals were intraperitoneally injected with a single dose of CCL\(_4\) and were killed 24 h later. Serum levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were measured to give an indication about the hepatic function. Moreover, malondialdehyde levels (indicative of lipid peroxidation), protein carbonyl groups (marker of protein oxidation) and the antioxidant enzymes activities were measured in the liver homogenate of the killed animals to assess the damage caused by CCL\(_4\) and the protective effects of the ethanol extract on liver tissues.\(^{14}\)

Serum levels of AST and ALT were considerably higher in the CCL\(_4\)-treated group as compared to the control group (proves the hepatotoxic effect of CCL\(_4\)) and were significantly lowered in the extract-pretreated group as compared to the CCL\(_4\)-treated group (indicates the hepatoprotective effect of *T. scandens* leaves in the prevention of hepatotoxin-induced acute liver injury). Similarly, levels of the biomarkers that denote lipid peroxidation and protein oxidation were much higher in the CCL\(_4\)-treated group than in the control group. Serum levels of AST and ALT were considerably higher in the CCL\(_4\)-treated group as compared to the control group (proves the hepatotoxic effect of CCL\(_4\)) and were significantly lowered in the extract-pretreated group as compared to the CCL\(_4\)-treated group (indicates the hepatoprotective effect of *T. scandens* leaves in the prevention of hepatotoxin-induced acute liver injury). Similarly, levels of the biomarkers that denote lipid peroxidation and protein oxidation were much higher in the CCL\(_4\)-treated group than in the control group. Furthermore, pretreatment with *T. scandens* ethanol extract had significantly reduced their levels in the extract-pretreated group. On the contrary, activities of the antioxidant enzymes were significantly reduced in the
CCl$_4$-treated group but were of normal levels for the extract pretreated animals. These findings proved that $T$. scandens extract has a significant protective effect against CCl$_4$-induced hepatotoxicity in rats, which may be due to its antioxidant properties.\cite{14}

**Antibacterial activity**

Muliyah et al.\cite{3} conducted an in vitro study to evaluate the antibacterial potential of the methanol extract of $T$. scandens' stem as a proposed mechanism for its antidiarrheal activity. Antibacterial activity was assayed on the Gram-negative bacilli *Escherichia coli* and the Gram-positive cocci *Staphylococcus aureus* following the well diffusion approach. Samples of different concentrations (25, 50, 75, and 100 mg/mL) were tested, using the solvent 10% dimethyl sulfoxide as the control and the antibiotic tetracycline as a positive control. All concentrations of $T$. scandens' stem extracts showed antibacterial activity against both *E. coli* and *S. aureus*, with the later more sensitive than the former (i.e., has larger inhibition zone).\cite{3} Moreover, Guzman and Padilla\cite{4} have reported the quorum sensing inhibitory activity to the methanol extract of $T$. scandens leaves against the Gram-negative bacteria *Chromobacterium violaceum*, with minimum quorum sensing inhibitory concentration (MQSIC) of 500 mg/mL as compared to the positive control (*Psidium guajava* extract), which have shown MQSIC of 125 mg/mL.

**Anti-human immunodeficiency virus activity**

Kwon et al.\cite{15} were the first to report the human immunodeficiency virus (HIV)-1 reverse transcriptase

| Study | Part under investigation | Medicinal activity/objective | Isolated metabolites | Remarks |
|-------|--------------------------|------------------------------|----------------------|---------|
| Lee et al.\cite{5} | Branch | Antidiabetic activity (glucose-uptake stimulant effect) | Genistein, 3',5'-diprenylgenistein, 6,8-diprenylgenistein, Derrone, Alpinumisoflavone | Genistein did not show glucose—uptake stimulant effect at all tested concentrations |
| Umar et al.\cite{2} | Leaves | In vivo study to confirm the antidiabetic activity | Both methanol and aqueous extracts have shown a significant fall in the fasting plasma glucose levels of alloxan-induced diabetic rats (as compared to glibenclamide) without inducing hypoglycemia in healthy nondiabetic rats. |
| Ahmed et al.\cite{11} | Leaves | Phytochemical analysis | Stigmasterol, Betulinic acid, Quercetin, Hypoletin, Isoscutellarein, Astragalin, Kaempferol | |
| Nguyen et al.\cite{12} | Leaves | Anti-gout (XO inhibition) | Quercetin, Kaempferol | It was a big study to investigate XO inhibitory potential of 96 Vietnamese medicinal plants |
| Nguyen and Nguyen\cite{13} | Stem | Characterization of XO inhibitory metabolites | Quercetin, Kaempferol, Tiliroside, Betulinic acid, Platanic acid, Emodin | Quercetin has shown higher XO inhibitory potential than allopurinol |
| Thanh et al.\cite{14} | Leaves | In vivo study to investigate the hepatoprotective and antioxidant properties | The ethanol extract of $T$. scandens leaves has shown a significant protective effect against CCl$_4$-induced hepatotoxicity in rats, which may be due to the antioxidant properties of its metabolites |
| Muliayah et al.\cite{3} | Stem | Antibacterial activity | All tested concentrations of the methanol extract of $T$. scandens' stem have shown significant antibacterial potential against *Escherichia coli* and *Staphylococcus aureus* |
| Kwon et al.\cite{15} | | HIV-1 reverse transcriptase inhibition | The ethanol extract of $T$. scandens has produced a dose-dependent inhibition of HIV-1 reverse transcriptase and virus production |
| Guzman and Padilla\cite{4} | Leaves | Anti-quorum sensing activity | The methanol extract of $T$. scandens leaves showed MQSIC of 500 mg/mL as compared to the positive control (*Psidium guajava* extract), which have shown MQSIC of 125 mg/mL |

XO = xanthine oxidase, MQSIC = minimum quorum sensing inhibitory concentration

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Table 1: Summary of the potential studies conducted on *Tetracera scandens*
(RTase) inhibition activity of the ethanol extract of *T. scandens*. Treatment of HIV-1-infected MT-4 cells with *T. scandens* extract has resulted in a dose-dependent inhibition of virus production with IC₅₀ values in the range of 2.0–2.5 µg/mL, suggesting a significant anti-HIV activity of the plant extract. An *in vitro* test was further performed using a RTase inhibition assay kit in order to evaluate the potential of *T. scandens* extract to inhibit viral RTase as a possible underlying mechanism of its anti-HIV effect. The extract inhibited HIV-1 RTase in a concentration-dependent manner, with an estimated IC₅₀ value of 0.7 µg/mL.

Table 1 summarizes the studies conducted on various parts of *T. scandens*, emphasizing the part investigated, the objective of the study as well as the isolated metabolites [Figure 2].

**CONCLUSION**

*T. scandens* is a traditional medicinal shrub that is widely used in Southeast Asia. Numerous indications have been reported to be managed by different parts of the plant, including DM, rheumatism, hypertension, hepatitis, urinary disorders, gout, snake bites, and diarrhea. Only few activities have been scientifically ascertained, including glucose-uptake stimulant activity, XO inhibitory activity, anti-quorum sensing activity, anti-HIV, antioxidant, and hepatoprotective activities. Flavonoids and terpenoids are the major phytochemical classes isolated from the plant.

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**Conflicts of interest**

There are no conflicts of interest.

**REFERENCES**

1. Tawan CS. *Tetracera scandens* (L.) Merr. In: van Valkenburg JLCH, Bunyapraphatsara N, editors. Plant resources of South-East Asia No. 12 (2): Medicinal and poisonous plants 2. Leiden, The Netherlands: Backhuys Publisher; 2001. p. 543.
2. Umar A, Ahmed QU, Muhammad BY, Dogarai BB, Soad SZ. Anti-hyperglycemic activity of the leaves of *Tetracera scandens* Linn. Merr. (Dilleniaceae) in alloxan induced diabetic rats. J Ethnopharmacol 2010;131:140-5.
3. Muliyah E, Sulistijorini S, Sulistyaningsih YC, Rafi M. Tetracera scandens as a medicinal plant: secretory structures, histochemistry, and antibacterial activity. J Trop Life Sci 2018;8:68-74.

4. Guzman JP, Padilla LV. Anti-quorum sensing activity of Tetracera scandens and Aleurites moluccana leaf extracts against Chromobacterium violaceum. Microbiol Res J Int 2017;22:1-10.

5. Lee MS, Kim CH, Hoang DM, Kim BY, Sohn CB, Kim MR, et al. Genistein-derivatives from Tetracera scandens stimulate glucose-uptake in L6 myotubes. Biol Pharm Bull 2009;32:504-8.

6. NParks Flora & Fauna Web. (n.d.). Available from: https://florafaunaweb.nparks.gov.sg/special-pages/plant-detail.aspx?id=5821. [Last accessed on 2018 Dec 10].

7. Flickr. (n.d.). Available from: https://www.flickr.com/photos/adaduitokla/5912765188/. [Last accessed on 2018 Dec 10].

8. Stuartexchange.org. (n.d.). Available from: http://www.stuartexchange.org/Malakatmon.html. [Last accessed on 2019 Aug 5].

9. Useful Tropical Plants. (n.d.). Available from: http://tropical.therfn.info/viewtropical.php?id=Tetracera+scandens. [Last accessed on 2019 Aug 6].

10. Lima CC, Lemos RPL, Conserva LM. Dilleniaceae family: An overview of its ethnomedicinal uses, biological and phytochemical profile. J Pharmacog Phytochem 2014;3:181-204.

11. Ahmed QU, Umar A, Taher M, Susanti D, Amiroudine MZAM, Latip J. Phytochemical investigation of the leaves of Tetracera scandens Linn. and in vitro antidiabetic activity of hypolein. In: Proceedings of the International Conference on Science, Technology and Social Sciences (ICSTSS) 2012. Singapore: Springer; 2014. p. 591-608.

12. Nguyen MT, Awale S, Tetzuka Y, Tran QL, Watanabe H, Kadota S. Xanthine oxidase inhibitory activity of Vietnamese medicinal plants. Biol Pharm Bull 2004;27:1414-21.

13. Nguyen MTT, Nguyen NT. A new lupane triterpene from Tetracera scandens L., xanthine oxidase inhibitor. Nat Prod Res 2013;27:61-7.

14. Thanh TB, Thanh HN, Minh HPT, Le-Thi-Thu H, Ly HDT, Duc LV. Protective effect of Tetracera scandens L. leaf extract against CCl4-induced acute liver injury in rats. Asian Pac J Trop Biomed 2015;5:221-7.

15. Kwon HS, Park JA, Kim JH, You JC. Identification of anti-HIV and anti-reverse transcriptase activity from Tetracera scandens. BMB Rep 2012;45:165-70.