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Thottea grandiflora: A Review on its Traditional Uses, Phytochemical Constituents and Pharmacological Actions

T. Balan, N.F. Muhamad Nizam, L. Rajendhiran, N.A.H. Ghazali, S. Murugesu, S. Fatinathan and V. Perumal*

Faculty of Pharmacy and Health Sciences, Royal College of Medicine Perak, Universiti Kuala Lumpur, Ipoh, Malaysia.

Thottea grandiflora is a plant commonly called "Hempedu Beruang" and is widely distributed in Peninsular Malaysia. *T. grandiflora* plant's part is used in folk medicine for health benefits such as fever, asthma, cough, diabetes, malaria, stomach disorder, back pain, and lung tumours. This plant has reported pharmacological activities like antidiabetic, anti-inflammatory, antimicrobial, antifungal, and antihyperglycemic. However, this plant is not much explored despite many traditional claims by the local tribes on the potential use of the plant. This study aimed to review the botanical characterisation, traditional uses, phytochemical constituents and pharmacological actions of *T. grandiflora*. This review is based on published electronic database literature on the traditional uses, pharmacology, and chemistry of *T. grandiflora*. The electronic databases used were Google Scholar, Science Direct, PubMed and Scopus. The plant parts can be further analysed for their clinical effects and utilised in pharmaceutical product development.

Keywords: phytochemical constituents; electronic database; pharmacological action; *T. grandiflora*; traditional uses

I. INTRODUCTION

Medicinal plants are plants that treat several diseases using traditional methods. Medical plants lead to the development of novel drugs owing to the presence of active phytoconstituents present in the plant matrices (Azwanida, 2015). The reported chemical constituents of plants are flavonoids, saponins, alkaloids and phenolics. These substances are said to impact individuals' and communities' health significantly. In addition, it is also used as an additive food for pregnant and nursing mothers for medical purposes (Edeoga *et al*., 2005).

According to WHO, nearly 80% of people worldwide rely on traditional medicines for health-related benefits. It is because this herbal medicine has fewer side effects than modern treatment (Ekor, 2014). As a result, Malaysia emerged as an alternative source because it is rich in is one of the medicinal plants reported to have important therapeutic values.

T. grandiflora is an ethnomedicinal plant from Peninsular Malaysia and belongs to the family Aristolochiacea. The genus *Thottea* (Aristolochiaceae) is distributed worldwide, including Malaysia, Sri Lanka, China, Bangladesh, Thailand, Myanmar, India, Philippines and Brunei (Yao, 2013). Similarly, other species, *Thottea beungongtanoeh,* is found at Acheh (Mustaqim & Arico, 2022).

It is locally known to have 35 species by the genus itself, some of namely *T. corymbosa, T. dependens, T. grandiflora, T. tricornis and T. siliquosa*. Notably, there are 16 species located in Malaysia (Salleh *et al*., 2023).

T. grandiflora, locally known as "hempedu beruang" grows in the primary rainforests of Malaysia. The vernacular names of this plant are Geroboh (English), Pokok Kerubut (Malay), Seburut (Malay), Sel-wohl (Semelai), Semubut (Malay), Sentondok Gajah (Malay), Seperuit (Malay), Telinga Kelawar by Malaysian Biodiversity Information System (Mybis) (Chua *et al*., 2006). *T. grandiflora* is an ethnomedicinal herb used by local tribals in Malaysia to treat various ailments, including lower back pain, lung, and stomach. It improves low sexual energy for men as well as relieves cough and

*Corresponding author's e-mail: vikneswari@unikl.edu.my

asthma (Burkill, 1966; Taysse *et al*., 1995; Mohammad *et al*., 2012).

Furthermore, *T. grandiflora* is also reported to possess diuretic properties (Daud *et al*., 2018). In addition, this plant has been classified as an anti-inflammatory plant. It has been scientifically proven to exhibit 5- 5-lipoxygenase inhibiting activity (Salleh & Khamis, 2021), antimycobacterial activity and relieves symptoms of tuberculosis (Sabran *et al*., 2018). From the literature, it has been found that this plant is not much explored despite many traditional claims by the local tribal on the potential use of the plant. Therefore, this article is intended to review the traditional uses, phytochemical constituents and pharmacological actions of *T. grandiflora*.

II. MATERIALS AND METHOD

This review compiles the information on the plant that has been reported from 1995 until 2023. The information includes the botanical aspects, traditional uses, phytochemical constituents and pharmacological use of the plant. Electronic searches were conducted and obtained from several websites such as PubMed, Scopus, Scientific Electronic Library Online (SCIELO), Google Scholar, Science Direct, Open Access Journals DOAJ, Springer Link, Research Gate and WILEY. The keywords used to search for the articles are *Thottea* genus, *Thottea grandiflora*, botany, traditional use, and phytochemical constituents of *T. grandiflora* plants. A total of 33 scientific papers have been used to review the traditional uses, chemistry and pharmacological activity of *T. grandiflora*.

III. RESULT AND DISCUSSION

A. The Genus of T. grandiflora

There are 22 Thottea species, seven of which have been found in Malaysia. The seven Thottea plants recognised in Malaysia are *T. grandiflora*, *T. piperiformis*, *T. sumatrana*, *T. tomentosa*, *T. parviflora*, *T. tricornis* and *T. dependens*. Interestingly, a few Thottea species were discovered recently by Universiti Putra Malaysia, which are *T. papilionis* and *T. anthonysamyi*. Apart from that, scientists also discovered *T. praetermissa* at Gunung Ledang, Asahan; *T. ruthiae* at Kampung La, Besut; *T. reflexa*, *T. terengganuensis* and *T. piscodora* at Terengganu (Yao, 2013).

B. Botanical Information of T. grandiflora

Figure 1 shows the image of *T. grandiflora* in Peninsular Malaysia. Table 1 shows the botanical aspects of *T. grandiflora*. It is more similar to *T. terengganuensis* based on the length of the width of the lamina, where they have densely pubescent lower lamina surface, stamens arranged in two whorls and lanceolate lamina with rounded base (Chua *et al*., 2006). However, it differs in its inflorescences at the stem base close to ground level.

Figure 1. The flowers of *Thottea grandiflora*.

The lamina base of *T. grandiflora* can be cordate, sometimes round, but rarely truncate. The exterior veins are white, while the bloom envelope is a dark claret colour. Perianth shape is bell-shaped, 3-lobed, such lobes oblong and rarely deltoid. Besides, the stamens can be 28-42 in two whorls. The upper whorl is range 12-18, and the lower whorl is 16-24. They support the plant's flower and protect it from unwanted insect attacks. *T. grandiflora* can usually be found in lowland and hill forests up to 600m with tall shrubs up to 2m (Nusaiba & Murugan, 2013; Sabran *et al*., 2016).

Table 1. Botanical information of *T. grandiflora*

Parts of the Plant	Characteristic
Lamina: length by width (cm)	Ovate, oblong, broadly lanceolate or oblanceolate: (16-)21.5-26(-43.5) by (6.5-)10.5-24(-26.5)
Lamina base	Cordate, sometimes rounded, rarely truncate

Inflorescences	At acils of foliage leaf or at nodes of stem below foliage leaves well above grounded level
Perianth shape	Dark claret-coloured, outside veins white
Perianth colour	Bell-shapes, 3-lobed; lobes oblong, rarely deltoid
Perianth length by diameter (cm)	(3-)6-14 by 6-10
Stamens	28-42 in 2 whorls; upper whorl 12-18, lower whorl 16-24
Stigmatic lobes number	10-15
Capsule indumentum	Villose

C. Traditional Use of T. grandiflora

The root of *T. grandiflora* can potentially treat fevers agues, invigorate and as a postpartum remedy. This was followed by an investigation on *T. grandiflora* plants from Bukit Bauk in Terengganu possess to treat malarial infection, postpartum tonic and to cure fever (Ghadin *et al.*, 2008). Another study mentioned that the root of this plant has several benefits on lung tumours, stomach tumours, fever, lower back pain, and body heat. It has been used in Temuan native villages used the plant to treat constipation, malaria, diabetes and tumours for ages (Ong *et al.*, 2011).

Furthermore, *T. grandiflora* root also has a lot of benefits in treating severe asthma (Mohammad *et al.*, 2012), diabetes, low sexual energy for men, cough and asthma (Sabran *et al.*, 2018). The traditional uses of the plant parts have been summarised in Table 2.

D. Phytochemical Constituents

The isolation of antidiabetic compounds from the roots *of T. grandiflora* was performed by Okechukwu (2011). The roots of *T. grandiflora* were extracted using dichloromethane, and the extract was fractionated into several fractions. The resulting fraction E and sub-fraction E1 recorded the presence of flavonoids, alkaloids, terpenoids and saponins. Sub-fraction E1 was then introduced into High Performance Liquid Chromatography (HPLC) profiling and showed the presence of five antidiabetic compounds: kaempferol (1), caffeic acid (2), quercetin (3), catechin (4), and berberine (5) that has been listed in Table 3.

Furthermore, Sabran *et al.* (2018) have identified bioactive compounds from the roots of *T. grandiflora* collected from Endau Rompin Johor National Park. The roots of *T. grandiflora* were extracted using hexane, ethyl acetate, absolute methanol, water and 80% methanol. The total compounds that were isolated from the roots of *T. grandiflora* were 21 compounds, which include acetic acid (6), hydroquinone (7), 2,3-dihydro-3,5-dihydroxy-6-methyl-4H-pyran-4-one (8), isosorbide (9), propanoic acid, 2-oxo-, methyl ester (10), 1-hydroxy-2-propane (11), glycerin (12), hexanohydroxamic acid (13), cis-2-methyl-3-(1-oxopropyl)-cyclopentanone (14), butyrolactone (15), phenol (16), (S)-(+)-3-hydroxytetrahydrofuran (17), methylpyrazine (18), oleic acid (19), n-hexadecanoic acid (20), 9,12-octadecadienoic acid, methyl ester, (E,E)- (21), 4-methylmannose (22), methylhydrazine (23), 2-furancarboxaldehyde, 5-(hydroxymethyl)- (24), 9,12,15-Octadecatrien-1-ol, (Z,Z,Z)- (25), and heptadecanoic acid (26).

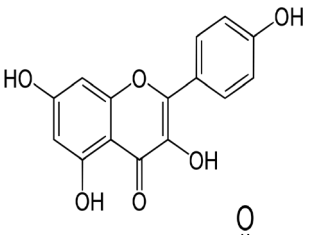
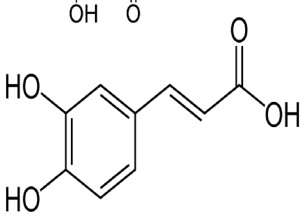
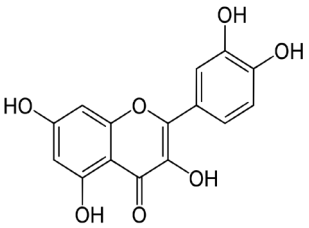
Kaempferol displayed antitumor activity against tumour cell apoptosis. Antioxidants activity was shown by an inhibition in DPPH and ABTS radical scavenging activity and anti-inflammatory activity against T-cell proliferation (Wang *et al.*, 2018). The compound also exhibited antidiabetic activity by activating AMP-activated protein kinase (AMPK) (Gothai *et al.*, 2016). This compound showed antimicrobial activity by decreasing the number of *Helicobacter pylori* colonies in the stomach of the gerbils and also cardiovascular protective effect where the mechanism may be related to the anti-inflammatory and antioxidant and properties by preventing the oxidation of the lipoprotein low-density lipoprotein (LDL) (Calderon *et al.*, 2011).

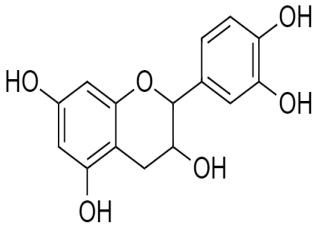
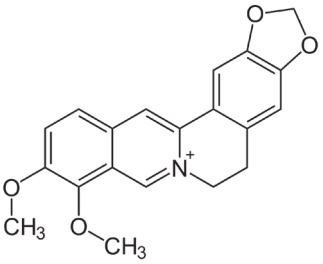
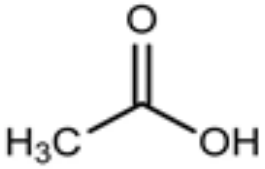
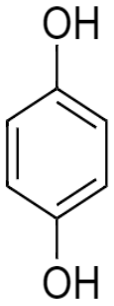
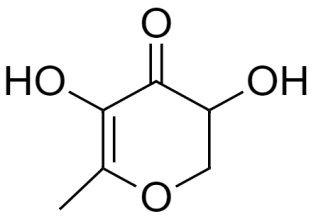
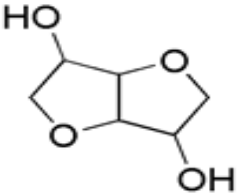
Table 2. Uses in traditional of medicine *T. grandiflora*

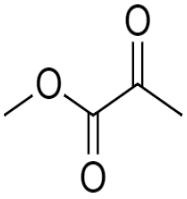
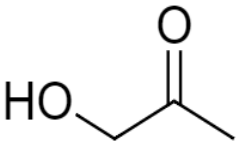
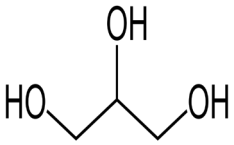
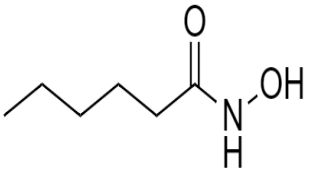
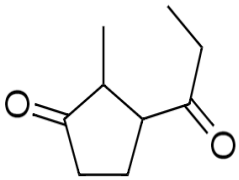
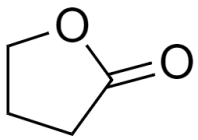
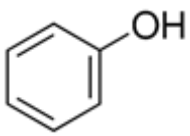
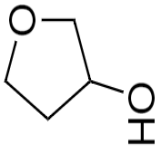
Place	Tribal	Part Used	Ethnomedical Used	Preparation	References
Bukit Bauk, Terengganu	N/A	Stem and Root	Postpartum tonic, cure fever, malarial infection	NA	(Ghadin *et al.*, 2008)
Kampung Jeram Kedah, Negeri Sembilan	Temuan	Root	Lung tumour, stomach tumour, fever, lower back pain, body heaty	NA	(Ong *et al.*, 2011)
Perdu Beruang	Kensiu	Root	Asthma	Decoction	(Mohammad *et al.*, 2012)
Endau Rompin, Johor	N/A	Root	Diabetic, low sexual energy for men, cough, asthma	NA	(Sabran *et al.*, 2018)
Endau Rompin, Johor	N/A	Root	Asthma, cough	NA	(Sabran *et al.*, 2018)

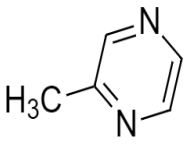
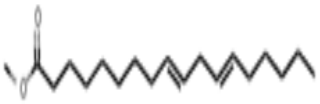
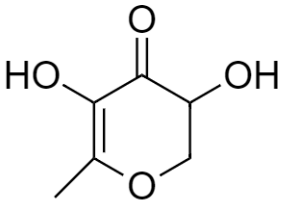
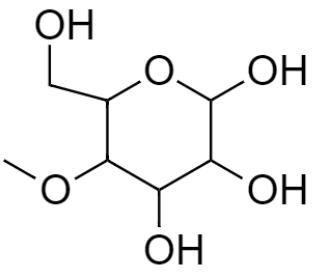
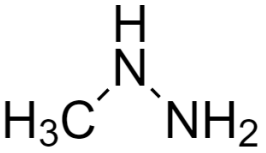
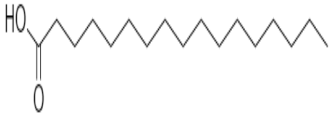
NA: Not applicable

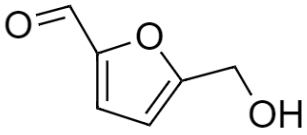
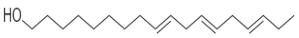
Table 3. List of bioactive compounds isolated from *T. grandiflora*

Name of compound	Structure	Activities	Part of plants and types of extract	References
Kaempherol (1)		Antitumor, antioxidants, antidiabetic, antimicrobial, anti-inflammatory.	Root and dichloro-methane	(Okechukwu, 2011)
Caffeic acid (2)		Antioxidant		
Quercetin (3)		Antidiabetic, antioxidant, antimicrobial, anti-inflammatory		

Catechin (4)		Anticancer, antioxidant		
Berberine (5)		Antimicrobial, anti-inflammatory, antidiabetic		
Acetic acid (6)		Antimycobacterial, antituberculosis, antibacterial	Root and water	(Sabran *et al*., 2018)
Hydroquinone (7)		Antimycobacterial, antituberculosis, antibacterial		
2,3-Dihydro-3,5-dihydroxy-6-methyl-4H-pyran-4-one (8)		Antimycobacterial, antituberculosis, antibacterial		
Isosorbide (9)		Antimycobacterial, antituberculosis, antibacterial		

Propanoic acid, 2-oxo-, methyl ester (10)		Antimycobacterial, antituberculosis, antibacterial
1-Hydroxy-2-propanone (11)		Antimycobacterial, antituberculosis, antibacterial
Glycerin (12)		Antimycobacterial, antituberculosis, antibacterial
Hexanohydroxamic acid (13)		Antimycobacterial, antituberculosis, antibacterial
Cis-2-methyl-3-(1-oxopropyl)-cyclopentanone, (14)		Antimycobacterial, antituberculosis, antibacterial
Butyrolactone (15)		Antimycobacterial, antituberculosis, antibacterial
Phenol (16)		Antioxidant
(S)-(+)-3-Hydroxytetrahydrofuran (17)		Antimycobacterial

Methylpyrazine (18)		Antimycobacterial, antituberculosis, antibacterial		
Oleic acid (19)		Antimycobacterial	Root and 80% methanol	(Sabran *et al*., 2018)
n-Hexadecanoic acid (20)		Antimycobacterial		
9,12-Octadecadienoic acid, methyl ester, (E,E)- (21)		Antimycobacterial		
4H-Pyran-4-one, 2,3-dihydro-3,5-dihydroxy-6-methyl- (22)		Antimycobacterial		
4-Methylmannose (23)		Antimycobacterial		
Methylhydrazine (24)		Antimycobacterial		
2-Furancarboxaldehyde, 5-(hydroxymethyl)- (25)		Antimycobacterial		

9,12,15-Octadecatrien-1-ol, (Z,Z,Z)- (26)		Antimycobacterial
Heptadecanoic acid (27)		Antimycobacterial

Caffeic acid compound was reported to possess excellent hepatoprotective activity to reduce liver damage caused by CCl4 intoxication in rat (Pérez *et al*., 2001). Caffeic acid also has a significant antioxidant activity with variable methods of the *in-vitro* assay such as 2,2-diphenylpicrylhydrazyl (DPPH), metal chelating activity, superoxide anion radical scavenging, ferric thiocyanate antioxidant activity and reducing power (Gülçin, 2006). This compound was also found to significantly lower blood glucose and glycosylated haemoglobin levels (Čerňáková & Košťálová, 2002).

Moreover, quercetin was reported to have antidiabetic property by suppressing the nuclear factor kappa B (NF-kB) system (Gothai *et al*., 2016). It also has been reported to have antioxidant activity against tert-butyl hydroperoxide-induced lipid peroxidation, antiviral activity against budding in MT2 cells, anticancer activity against growth in breast tumours and antimicrobial activity against *Listeria monocytogenes, Escherichia coli* and *Salmonellae enterica* (Maalik *et al*., 2014). The *in vivo* anti-inflammatory study shows a depletion in the utterance of inflammatory genes, hepatoprotective activity against non-alcoholic steatohepatitis gerbils, neurological effects and cardiovascular protection against isolated rat arteries (Maalik *et al*., 2014).

The *in vitro* antidiabetic potential was exhibited through suppression the activation of NF-kB system via the suppression of proinflammatory cytokines productions (Gothai *et al*., 2016). This compound was also reported to significantly affect anticancer activity against various cancer cells, such as hep G-2, HCT 116, and HCT 15 (Manikandan *et al*., 2012). The compound of catechin extracted from red grape possess antioxidant activity, which was evaluated by the DPPH and radicals generated from the peroxynitrite degeneration. In addition, the bioactive berberine has antimicrobial activity isolated from *Mahonia aquifolium* plant (Čerňáková & Košťálová, 2002). Besides that, berberine was reported to possess antioxidant, anti-inflammatory, and antidiabetic activities significantly (Li *et al*., 2014).

Furthermore, hydroquinone, acetic acid, 2,3-dihydro-3,5-dihydroxy-6-methyl-4h-pyran-4-one, isosorbide, propanoic acid, 2-oxo-, methyl ester and 1-hydroxy-2-propane bioactive compounds were reported to have several activities such as antimycobacterial, antituberculosis and antibacterial (Sabran *et al*., 2018). Hydroquinone has potency in photosynthetic inhibitors to produce sorgoleone (Weston & Czarnota, 2001) and potency in cytotoxicity on cultured rat hepatoma cells (Assaf *et al*., 1987).

Glycerine was formulated into glycerine suppositories and was introduced into premature infants to improve the bowel movement of infants (Patel *et al*., 2017). Other than that, several compounds that were found to have antimycobacterial include hexanohydroxamic acid, cis-2-methyl-3-(1-oxopropyl)-cyclopentanone and butyrolactone (Okechukwu, 2011).

Phenol compounds were reported to have antioxidant activity via redox reaction. Phenol is said to have slight toxicity activity on the nonspecific cytotoxic cells (NCC) due to the presence of the hydrophilic group in the structure of phenol (Taysse *et al*., 1995; Johari *et al*., 2019; Soobrattee *et al*., 2005; Khong, 2019;). However, it was reported to have toxicity activity and be harmful towards living organisms (Michalowicz & Duda, 2007).

The (s)-(+)-3-hydroxytetrahydrofuran, methylpyrazine, oleic acid, n-hexadecanoic acid, 9,12-octadecadienoic acid, methyl ester, (e,e)-, 4-methylmannose,methylhydrazine, 2-furancarboxaldehyde, 5-(hydroxymethyl)-, 9,12,15-Octadecatrien-1-ol, (z,z,z)- and heptadecanoic acid possesses an antimycobacterial activity. The presence of these compounds in 80% of methanol extract inhibits bacterial growth (Sabran *et al*., 2018).

E. Pharmacological Activities

1. Anti-inflammatory activity

The pharmacological activities of *T. grandiflora* have been studied by researchers consistently for the past few years to prove the claims of its medicinal value and further evaluate the potency of this plant from different parts used to prevent and treat diseases. In mice, the anti-inflammatory effects of *T. grandiflora* plant extract was reported using tetradecanochoracetic acetate (TPA) oedema. In this study, the leaf extract of this plant exerted a high inhibition (80%) when the extract was administered topically (2mg/kg) 40 minutes before inducing oedema with TPA. Nevertheless, the extracts of *T. grandiflora* administered intravenously at 200mg/kg doses failed to show any inhibition in the model. Therefore, this TPA model concluded that *T. grandiflora* plant extract displayed a high anti-inflammatory effect when administered topically (Mustapha *et al*., 2001).

2. Antimicrobial activity

The ethyl acetate extract of the *T. grandiflora* stems collected at Bukit Bauk, Terengganu, Malaysia, had significant antimicrobial activity. The study has shown that the extract was active against pathogenic bacteria with prominent inhibition zones (mm), such as *Bacillus subtilis* (17 mm), *Bacillus cereus* (22 mm), *Pleisiomonas shigelloides* (20 mm) and *Pseudomonas aeruginosa* (20 mm). Besides, these plant extracts also possessed antifungal activity measured by the percentage of inhibition against *Pythium ultimum* (20%), *Geothrichum candidum* (23%), *Phytophthora erythroseptica* (23%), *Aspergillus fumigatus* (44%) and *Fusarium solani* (62%) (Ghadin *et al*., 2008).

3. Anti-hyperglycaemic activity

The first attempt to study the anti-hyperglycaemic activity of purified extract of *T. grandiflora* was performed using the plant's roots (Okechukwu, 2011). A preliminary pharmacological study revealed that the dichloromethane (DCM) crude root extracts possess antidiabetic activity. In this study, fractions A-E were obtained from partial purification of root extracts. For four weeks, further purified sub-fractions E1, E2 and E3 were appraised for their antidiabetic effect using streptozotocin (STZ)-induced rats. The blood glucose level and body weight of the diabetic rats were determined at week 0 and week 4. Fraction E and sub-fraction E1 significantly lowered the blood glucose level in diabetic rats by an average of 32.13% and 44.63%. The high-performance liquid chromatography (HPLC) profiling of fraction E and sub-fraction E1 composed the appearance of alkaloids, flavonoids, quercetin, kaempferol, catechin and caffeic acid, which have been reported to possess antidiabetic activity.

4. Antimycobacterial activity

Sabran *et al.* (2018) investigate the antimycobacterial activity of extracts such as ethyl acetate, hexane, absolute methanol, water and 80% methanol root extracts of plant *T. grandiflora*. The collected roots at Endau Rompin Johor National Park, Malaysia were screened for their major phytochemical constituents using gas chromatography mass spectrometry (GCMS) analysis. The root is composed of 11 major constituents that exhibit the antimycobacterial activity. The crude ethyl acetate extract of *T. grandiflora* exhibited the largest inhibition zone on *Mycobacterium smegmatis* at 100 mg/ml (14.92 ± 0.86 mm), followed by 80% methanol and ethyl acetate extracts.

IV. FUTURE RECOMMENDATION

The current study has successfully defined the traditional use, phytochemical constituents, and pharmacology activity of *T. grandiflora*. However, it also highlights several areas where further research is needed to fully understand the therapeutic potential of this plant to be utilised in pharmaceutical and nutraceutical. While numerous bioactive compounds have been identified in *T. grandiflora*, there is a lack of comprehensive pharmacological studies elucidating the mechanisms by which these compounds exert their effects. Future research should focus on conducting comprehensive pharmacological investigations on better understanding *T. grandiflora's* mechanism to be utilised for therapeutic purposes. The *in vitro* studies are recommended to further characterise and validate the reported antimycobacterial, antituberculosis, and antibacterial effects of *T. grandiflora*. The future research should involve testing the plant extracts

or isolated compounds against specific pathogens in laboratory settings to assess their therapeutic effects. The antioxidant activity of *T. grandiflora* should be evaluated through both *in vitro* and *in vivo* studies. This would help determine its potential role in combating oxidative stress-related diseases and provide insights into its mechanism of action as an antioxidant agents. A comprehensive toxicity studies are imperative to evaluate *T. grandiflora* safety profile before its utilisation for therapeutic purposed. These studies would identify any potential adverse effects or toxicity associated with the consumption or application of *T. grandiflora* extracts or products. Future research could employ a metabolomics approach to identify the metabolic pathways affected by *T. grandiflora* and elucidate its mechanism of action. This would involve profiling the plant's metabolites and understanding its interaction with biological systems, providing valuable insights into its pharmacological effects. In summary, further research is warranted to fully explore the therapeutic potential of *T. grandiflora*, including conducting detailed pharmacological studies, evaluating its antimicrobial and antioxidant activities, assessing its safety profile, and employing advanced analytical techniques to elucidate its mechanism of action. These efforts could ultimately lead to the development of novel therapeutic agents derived from *T. grandiflora* for the treatment of various diseases.

Table 4. Information on pharmacological activities, parts of *T. grandiflora*, types of extracts used and location of plant collection

Activity	Part	Type of extract	Location of collection	References
Anti-inflammatory	Leaves	NA	NA	Mustapha *et al.*, 2001)
Antimicrobial, antifungal	Stem	Ethyl acetate	Bukit Bauk, Terengganu, Malaysia.	(Ghadin *et al.*, 2008)
Antihyperglycemic	Root	Dichloromethane	NA	(Okechukwu, 2011)
Antimycobacterial	Root	Ethyl acetate	Endau Rompin Johor National Park, Malaysia	(Sabran *et al.*, 2018)

V. CONCLUSION

In conclusion, *T. grandiflora* possesses various pharmacological potential including anti-inflammatory, antimicrobial, antifungal, antihyperglycemic and antimycobacterial. The plant parts can be further analysed for their clinical effects and utilised in pharmaceutical product development.

VI. CONFLICT OF INTEREST

The authors declare that they have no competing financial interests or known personal relationships which could have seemed to influence the work reported in this article

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