Coscinium fenestratum: A Review on Phytochemicals and Pharmacological Properties

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Contents

Abstract

Coscinium fenestratum has been used in the traditional medicine, especially in the Ayurvedic method of healing as this plant can be found vastly in the Western Ghats of India. The distribution of this plant is concentrated to the Southeast Asia

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including Sri Lanka, India, Cambodia, Vietnam, Peninsular Malaysia, Sumatra, West Java, Borneo, Northeast of Thailand and Laos. This review is related to the phytochemicals and pharmacological effects of *C. fenestratum*. The major chemical constituents present in this plant include alkaloids, flavonoids and steroids. The most important bio-active compound is the berberine, which is the most widely studied plant compound. This plant exerts several pharmacological effects including antidiabetic, anticancer, antibacterial, antimalarial, antioxidant, antihypertensive, antiulcer, neuroprotector and wound healing activities. This chapter is supported by in vitro and in vivo studies carried out from the year of 1970 to 2016, which are available from PubMed, ScienceDirect, Google Scholar and Scopus.

Keywords
Antidiabetic · Berberine · *Coscinium fenestratum* · Pharmacology · Phytochemicals

5.1 Introduction

Coscinium fenestratum Syn. *Menispermum fenestratum* (Menispermaceae) is also known as tree turmeric. It is a forest plant discovered to exhibit many therapeutic indications. *Coscinium fenestratum* (Gaertn.) Colebr. is a liana species (Kathriarachchi et al. 2004; Hassler 2016). Traditionally, this plant is widely used in the Indian systems of medicines, such as the Ayurveda and Siddha, and is known as Kalambaka or Dāru-haridrā (Sanskrit) (Rao 1985), Jhaar-ki-hald (Hindi), Maramanjal (Malayalam) and Manu pasupu (Telugu) (Sumy et al. 2000). In some studies, *C. fenestratum* was proven to exhibit antidiabetic (Shirwaikar et al. 2005), anticancer (Ueda et al. 2002) and anti-gonococci activities (Chomnawang et al. 2009). The plant is also used in curing microbial infections in the folk medicine of India and Indonesia (Siwon et al. 1980). Therefore, this article objective is to review on *C. fenestratum* regarding its phytochemicals and pharmacological properties.

Reviews on *C. fenestratum* were retrieved between 1970 and 2016 using various scientific search engines, such as PubMed, ScienceDirect, Google Scholar and Scopus. The research emphasized on the phytochemical investigation and pharmacological properties of *C. fenestratum* both in vivo and in vitro are considered for discussion in this chapter. The keywords used are '*Coscinium fenestratum*' and 'berberine'. The literature review suggested that most of the studies on *C. fenestratum* were conducted in India, Thailand, China and Malaysia.

5.2 Characteristics of *Coscinium fenestratum*

C. fenestratum is a member of Menispermaceae family, which is a climber as it can climb onto high trees with strong woody stems (Kessler 1993). The leaves are alternate and have downy petioles. It also has obtuse heart-shaped leaves (Fig. 5.1a), 3–9

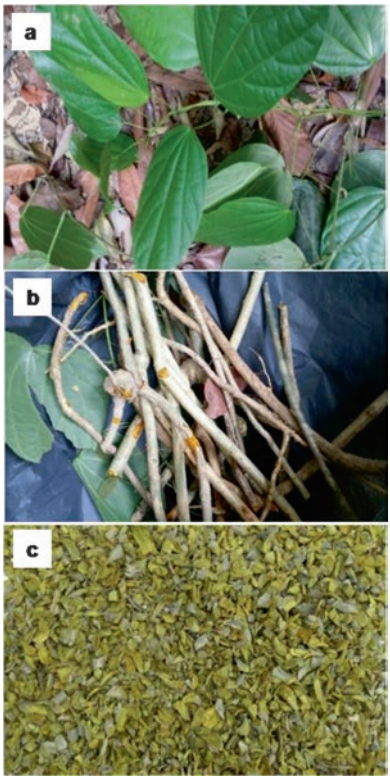

Fig. 5.1 *Coscinium fenestratum*; (**a**) leaves; (**b**) stems; (**c**) dried and powdered stems

inches long and 2–6 inches broad, with smooth and shiny upper surface and very hoary lower part. Besides that, the flowers are numerous with globular heads and villous and green in colour (Rao 1985). The stem is yellowish-brown at the outside and yellow in the inside (Fig. 5.1b, c). *C. fenestratum* is a unisexual and dioecious plant by which the male and female reproductive organs are separated.

5.3 Distribution of *Coscinium fenestratum*

C. fenestratum is widely distributed in Sri Lanka, India, Cambodia, Vietnam, peninsular Malaysia, Sumatra, West Java, Borneo, Northeast of Thailand and Laos (Hassler 2016). This species is mostly concentrated in the Western Ghats of India, especially in the high rainfall, wet evergreen and semievergreen forests (Sumy et al. 2000). It had been used for centuries in the Ayurveda method of healing, in which roots and stems are the crucial parts with medicinal properties. A study conducted in Sri Lanka found that the suitable condition for the growth of *C. fenestratum* is the lowland wet zone habitat, and it can grow well when it receives enough light supply (Kathriarachchi et al. 2004).

5.4 Phytochemicals of *Coscinium fenestratum*

A number of alkaloids are present in *C. fenestratum,* such as berberine (**1**), jatrorrhizine (**2**) and palmatine **(3)** (Fig. 5.2) (Siwon et al. 1980; Garcia et al. 1970). Siwon et al. (1980) also reported the presence of berberrubine **(4)**, thalifendine **(5)** and N, N-dimetyl-lindcarpine **(6)**(Fig. 5.2). Berberine (**1**) and jatrorrhizine (**2**) are the major components isolated from acid extraction of *C fenestratum*. Rojsanga et al. (2006) reported that berberine (**1**) is the major component of *C. fenestratum* when extracted using 80% ethanol (Rojsanga 2006). Berberine **(1)** is an isoprenaline alkaloid which has significant medicinal benefits such as antidiabetic, antiproliferative and antibacterial activities. Tran et al. (2013) also discovered alkaloid compounds such as jatrorrhizine **(2)** and columbamine **(7)** in *C. fenestratum* (Fig. 5.2).

Findings from a study performed by Goveas and Abraham (2013) supported Rojsanga et al. (2006) that the main component obtained from extraction of *C. fenestratum* stem is berberine **(1).** Goveas and Abraham (2013) also found that *C. fenestratum* methanolic extract contained significant amount of phenols and flavonoids with the value of 18.35 ± 0.56 mg GAE/g extract (mg of gallic acid equivalent per gram of extract) and 12.8 ± 0.88 mg QE/g extract (mg of quercetin equivalent per gram of extract), respectively. Okechukwu et al. (2010) reported that polyphenols contained in the *C. fenestratum* extract are rutin **(8)**, quercetin **(9)** and kaempferol **(10)** based on HPLC profiling (Fig. 5.2). Furthermore, *C. fenestratum* extract is also comprised of saponins, glycoside and terpenoids.

Madhavan et al. (2014) carried out a study on discarded *C. fenestratum* leaves from Ayurveda manufacturing to determine the presence of active ingredients in the leaf extract. The study was carried out by using HPLC, infrared (IR) spectrum and liquid chromatography-mass spectrometry (LC-MS). It was detected that 0.12% of the leaf extract in butanone contains ecdysterone **(11)** and berberine **(1)**(Fig. 5.2). Although the percentage of ecdysterone **(11)** was higher in stem (0.22%) compared to leaves (0.12%), this study proved that the leaves of *C. fenestratum* also exhibit medicinal effect and should not be discarded as a waste (Madhavan et al. 2014). Ecdysterone **(11)** is an insect-metamorphosing steroids isolated from plants. This bio-active ecdysterone **(11)** was claimed to have a suppressive effect on hyperglycaemia induced by several hyperglycaemic agents which is important in treating diabetic patients (Yoshida et al. 1971). Other than its antidiabetic property, ecdysterone **(11)** also presented antitumor activity (Konovalova et al. 2002).

5.5 Pharmacological Activities of *Coscinium fenestratum*

5.5.1 Antidiabetic Activity

There are two types of diabetes mellitus; type 1 diabetes mellitus is due to autoimmune destruction of insulin secreting cells in the islet of Langerhans, which impair insulin secretion. Thus, glucose cannot be broken down properly and leads to

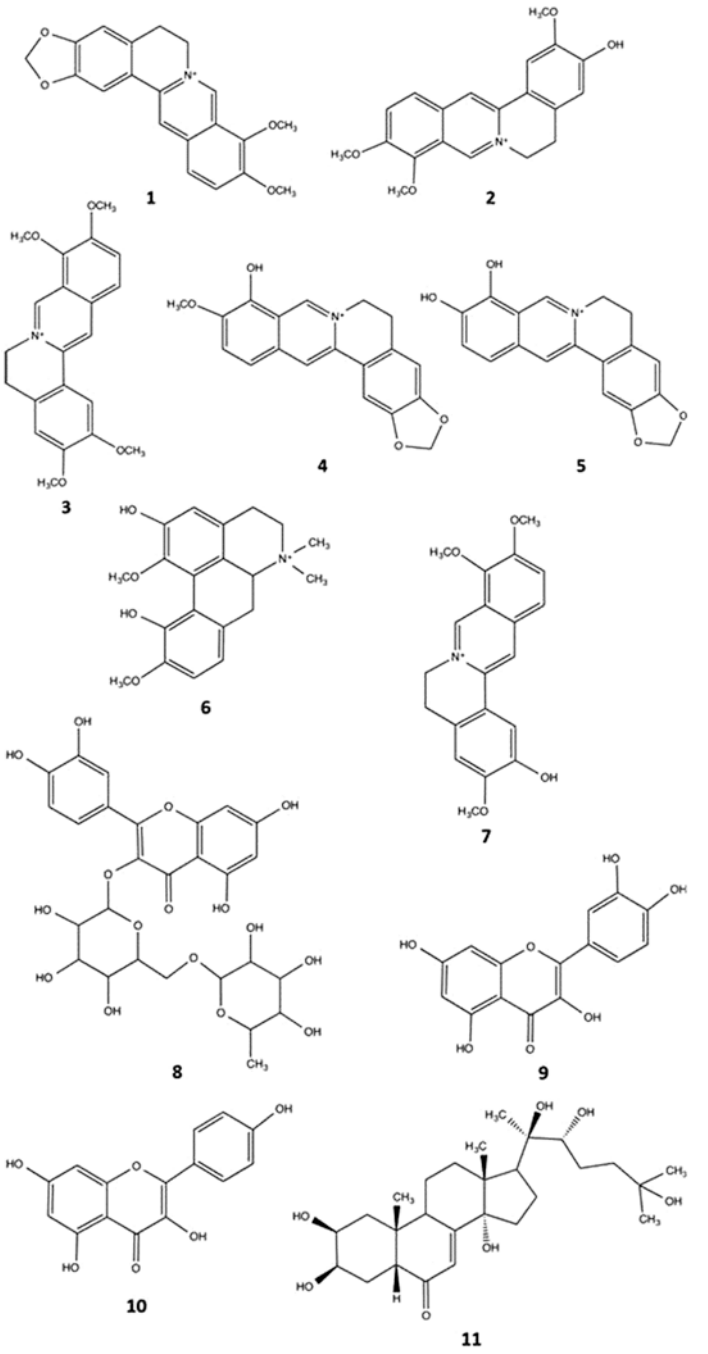

Fig. 5.2 Major phytochemicals of *Coscinium fenestratum*

hyperglycaemia. Meanwhile, type 2 diabetes mellitus is a common occurrence in obese patients of 40–70 years of age, mainly because of the resistance to insulin action (Baquer et al. 1998).

Shirwaikar et al. (2005) reported that hypoglycaemic effect of the *C. fenestratum* was not related to insulin secretion. Punitha et al. (2005) found that alcoholic extract of *C. fenestratum* significantly increased glucokinase and glucose-6-phosphate dehydrogenase (G6PD) level; however it decreased glucose-6-phosphatase (G6Pase) level in diabetic rats. Since it was proven in many studies that the major ingredient in *C. fenestratum* is berberine, thus, it is assumed that the hypoglycaemic effect is due to berberine. Singh and Kakkar (2009) reported that berberine did improve the condition of induced diabetic rats by improving glucose metabolism as it increases the action of glucokinase and G6PD. Hexokinase or glucokinase is an enzyme that is responsible for glycolysis process which acts directly on the breakdown of glucose and induces the removal of glucose from blood. Meanwhile, G6PD converts glucose-6-phosphate (G6P) into pentose sugar to increase the utilization of glucose, which occurs in pentose phosphate pathway (PPP). Moreover, **Xia** et al. (2011) stated that berberine is able to inhibit hepatic gluconeogenesis by reducing phosphoenolpyruvate carboxykinase (PEPCK) and G6Pase. Subsequently, this decreases glucose synthesis and hence subsides the blood glucose level. They also suggested that both enzyme reductions were the consequences of mRNA reduction which is independently caused by insulin since mRNA of PEPCK and G6Pase was also decreased when supplemented with berberine.

5.5.2 Anti-cancer Activity

5.5.2.1 Colorectal Cancer

Rojsanga et al. (2010) reported that berberine extracted from *C. fenestratum* had anti-proliferative effect against human colorectal carcinoma cell lines HCT-116 and SW480. *C. fenestratum* extraction was done in 80% ethanol (80ET), and dichloromethane (DCM) and water fraction (WF) were derived. In cell proliferative analysis, HCT-116 cell lines were tested with 10–100 μg/ml of 80ET and WF, 1–100 μg/ml of DCM and 1–50 μM of berberine for 24, 48 and 96 hours. Cell viability significantly reduced at the highest dose treatment at 96 hours. This result indicated that the inhibition of HCT-116 cell growth was dose- and time-dependent. In the Western blot analysis, NSAID-activated gene 1 (NAG-1), activity transcription factor 3 (ATF3) and cyclin DI expression in HCT-116 and SW480 were tested with berberine, DCM, 80ET and WF for 24 hours (Rojsanga et al. 2010). In the HCT-116 cell line, the Western blot result showed that *C. fenestratum* extract and its fraction and berberine induced the expression of NAG-1 and ATF3 of the cancer cells; however cyclin DI expression was suppressed. Both NAG-1 and ATF3 expressions were able to interrupt cancer cell growth and enhanced apoptosis; meanwhile suppression of cyclin DI expression prevents cancer cell to continue from growing. Thus, all those treatment were useful to inhibit HCT-116 cancer to spread. In contrast, Western blot

result for SW480 cancer cell, NAG-1 and ATF3 expression only stimulated in DCM-treated sample while cyclin D1 expression able to be suppressed in all treatment. Hence, previous study suggested that DCM fraction of *C. fenestratum* may be considered as the most appropriate treatment for cancer management (Rojsanga et al. 2010).

5.5.2.2 Lung Cancer

A study conducted by Ueda et al. (2002) discovered that methanol and methanol-water extract of *C. fenestratum* showed the potent anti-proliferative action on two lung carcinoma cells which are A549 and LLC. Methanol extract of *C. fenestratum* showed EC_{50} of 1.65 μg/ml against LLC. Meanwhile, the methanol-water extract of *C. fenestratum* presented EC_{50} of 2.88 μg/ml and 2.84 μg/ml against A549 and LLC, respectively. They also discovered that the cytotoxic effect of *C. fenestratum* was selective against lung-related tumour cancer cells and in turn can inhibit lung cancer cells to metastasize. Other than A549 and LLC, berberine also showed the cytotoxic effect against NCI-H838 (non-small cell lung adenocarcinoma). NCI-H838 treated with 100 μM of berberine showed higher apoptotic cells compared to 80 μM berberine concentration, which showed that berberine action was dose-dependent. From the study, berberine action also was found to be time dependent since the IC_{50} value at 72 hours was lower than IC_{50} value at 24 hours, which indicated that the potency of cytotoxic effect was higher in 72 hours compared to 24 hours.

From the similar study, Tungpradit et al. (2011) discovered that the apoptotic effect of NCI-H838 was related to Bcl-2 protein, caspase activity pathway and G2/M phase arrest. The Bcl-2 protein (anti-apoptotic) level decreased when treated with berberine; consequently the release of cytochrome C from mitochondria induced apoptosis. Besides that, the result presented that procaspase 7 was decreased and in turn increased caspase 7 when treated with berberine. This result suggested that procaspases 3, 6, 7 and 8 were decreased because they were converted to their active form, caspases 3, 6, 7 and 8, which are able to induce apoptosis against NCI-H838 cell lines. Moreover, berberine is also able to suppress NCI-H838 cell growth at G2/M phase and lead to apoptosis.

5.5.2.3 Human Head and Neck Cancer

The effect of *C. fenestratum* extract against human head and neck cancer cell lines (HN31) has been studied by Potikanond et al. (2015). HN31 is a metastatic lymph node squamous cell carcinoma of the pharynx. Cytotoxic effect of *C. fenestratum* was observed at the concentration of 1 mg/ml or higher compared to 5-Fluorouracil (5-FU) where the effect was observed at all concentration tests. However, *C. fenestratum* extract showed its maximal effect at concentration of 2.5 mg/ml compared to 5-FU at 10 mg/ml. The IC_{50} values of *C. fenestratum* extract and 5-FU after a 48-hour incubation were 0.12 mg/ml and 6.6 mg/ml, respectively. Since *C. fenestratum* extract has lower IC_{50} than 5-FU, this study suggested that *C. fenestratum* was more potent against HN31 cell lines (Potikanond et al. 2015). Moreover, the combination of *C. fenestratum* extract and 5-FU did not show any synergistic effect. They

discovered that *C. fenestratum* cytotoxic action was mediated via modulation of p38 mitogen-activated protein kinase (p38 MAPK), pAkt (tumour survival molecule) and p53 protein (tumour suppressor molecule). Thus, *C. fenestratum* extract decreases phosphorylation of p38 MAPK and pAkt expression. However, *C. fenestratum* extract increases p53 protein in a dose-dependent trend, which inhibits the survival of HN31 cancer cells and increases apoptosis.

5.5.2.4 Bile Duct Cancer

The treatment of bile duct cancer or cholangiocarcinoma is difficult, and the surgery is mostly offered to the patients. From the study conducted by He et al. (2012), they discovered that berberine is able to decrease cell viability and perform cytotoxic effect against human cholangiocarcinoma QBC939 cells, and it has minimal effect on normal human intrahepatic biliary epithelial cells (HIBEC) that showed its benefit outweighs the risk (He et al. 2012). Mechanisms of action of berberine in dealing with cholangiocarcinoma included G1 phase QBC939 cell cycle arrest, decreasing the expression of cyclin (CyclinD1) and cyclin-dependent protein kinases (Cdk2 and Cdk4) with concurrent increase in potent cyclin-dependent protein kinase inhibitor (p21 and p37) in QBC939 cell and inducing apoptosis and affecting the level of Bcl-2 family of proteins in QBC939 cancer cell line. Further test was performed by using Western blot to detect Bcl-xL, Bcl-2 and Bax in the cell treated with different concentrations of berberine. From the reduction of anti-apoptotic proteins (Bcl-xL and Bcl-2) with simultaneous induction of pro-apoptotic protein (Bax), it was shown that berberine is dose-dependent which means higher dose of berberine contributed to the higher number of cell cancer apoptosis (He et al. 2012).

5.5.3 Antibacterial Activity

5.5.3.1 Against *Neisseria gonorrhoeae*

According to Chomnawang et al. (2009), *C. fenestratum* has good inhibitory effect against *Neisseria gonorrhoeae*. *N. gonorrhoeae* is a Gram-negative diplococci and is associated with sexually transmitted disease (STD) which is spread by sexual contact or during giving birth where this bacteria can infect newborn baby. The results obtained from the study discovered that *C. fenestratum* was one of the effective plant extract against *N. gonorrhoeae* with minimum inhibitory concentration (MIC) value of 47.39 g/ml. Moreover, the finding from bioautographic assay also proved that *C. fenestratum* methanolic crude extract was an effective anti-gonococci when a large clear zone on the sample was exposed which indicated inhibition of *N. gonorrhoeae* growth. This bioautographic chromatogram was also conducted on pure berberine and ceftriazone. The inhibition zone on the agar appeared at the same position as the R value of pure berberine which suggested that the active compound against *N. gonorrhoeae* of *C. fenestratum* was berberine.

5.5.3.2 Against *Propionibacterium acnes* and *Staphylococcus epidermidis*

Berberine also demonstrated its effect on two types of skin microbes which are *Propionibacterium acnes* and *Staphylococcus epidermidis*. *P. acnes* and *S. epidermidis* are the normal flora on the skin, and they do not show any virulence effect if they are not induced. *P. acnes* is related to the common skin disease acne. However, *P. acnes* is an opportunistic pathogen which can cause postoperative and device-related infection (Perry and Lambert 2011). Meanwhile, *S. epidermidis* is related to nosocomial infection that is caused by device contamination during insertion and may lead to sepsis or endocarditis (Uckay et al. 2009). A study was carried out by Kumar et al. (2007), and the findings showed that *C. fenestratum* was able to inhibit the growth of both bacteria. The MIC values against both microbes were 0.049 mg/ml; meanwhile the minimum bactericidal concentration (MBC) values were 0.049 and 0.165 mg/ml against *P. acnes* and *S. epidermidis*, respectively. The bioautography assay also showed strong inhibition against the growth of *S. epidermidis* with prominent cleared zone on the disc; however the cleared zones were noticed to appear in a separate manner which indicates that more than one antimicrobial agent is observed in *C. fenestratum* ethanolic extract. One of the agents was berberine which is the major constituent of *C. fenestratum* (Kumar et al. 2007).

5.5.4 Antimalarial Activity

The main cause of malaria is *Plasmodium falciparum*, and it shows the most severe clinical disease compared to other plasmodium species such as *P. ovale*, *P. vivax*, *P. malariae* and *P. knowlesi.* Most of the human malaria is related to the infected anopheles mosquitoes which carry *P. sporozoites* and transmit the parasite to humans via a bite. This parasite infects the red blood cells and causes red blood cell confiscation in various organs such as the brain, lungs and placenta (Beeson and Brown 2002). Children and pregnant women have high risk of getting infected with *P. falciparum*.

An in vitro study have been conducted by Tran et al. (2013) to test the antimalarial effect of several traditional medicine plants against the growth of chloroquine-resistant *P. falciparum* FCR-3. The finding of the study is that all three *C. fenestratum* extracts (water, methanol and methanol-water) showed strong antimalarial effect against *P. falciparum*. *C. fenestratum* methanolic extract showed the strongest effect compared to the other extraction with EC_{50} of 0.5 μg/ml. Methanolic extract of *C. fenestratum* undergone a further test via activity-guided fractionation to isolate the active constituent that is responsible for the antimalarial effect. From the test result, they isolated berberine **(1)**, jatrorrhizine, **(2)** and columbamine **(3)** which then again gone through an in vitro study in their pure form. All three constituents berberine **(1)**, jatrorrhizine, **(2)** and columbamine **(3)** showed strong antimalarial effect with EC_{50} values of 1.3, 1.9 and 2.8 μM, respectively (Tran et al. 2013). Chloroquine was found to be the most effective drug in treating malarial and had been used vastly to

treat that disease and subsequently gave rise to chloroquine-resistant malarial (Wellems and Plowe 2001). Hence, *C. fenestratum* extract should be considered as the treatment for chloroquine-resistant malaria since the result from the study conducted by Tran et al. (2013) showed that *C. fenestratum* extract was able to possess strong anti-plasmodium activity.

5.5.5 Antioxidant Activity

Antioxidant properties of the *C. fenestratum* were tested by Goveas and Abraham (2013) by using 1,1-diphenyl-2-picryl-hydrazyl (DPPH) and 2,2′-azino-bis (3-ethy lbenzothiazoline-6-sulphonic acid) (ABTS) radical scavenging assay. In DPPH antioxidant assay, the ability of *C. fenestratum* stem and leaf extract to reduce DPPH was measured. The result revealed that methanolic extract of *C. fenestratum* stem exhibited higher antioxidant activity compared to the methanolic leaf extract of *C. fenestratum*. The highest value of DPPH scavenging activity in the methanolic stem extract was 71.3 ± 0.36% at concentration of 256 μg/ml, whereas the highest DPPH scavenging value in the methanolic leaf extract was 49 ± 0.88% at concentration of 512 μg/ml. Both methanolic stem and leaf extract were able to show DPPH scavenging activity at the minimum concentration of 2 μg/ml. They proposed that the significant scavenging activity of the *C. fenestratum* extract against DPPH is most probably interrelated with the present number of hydroxyl group. In ABTS radical scavenging assay, the radical scavenging activity of *C. fenestratum* stem extract ranges from 9.3 ± 0.56% to 69.3 ± 1.76%; meanwhile the leaf extract has a scavenging activity of 3.6 ± 0.27% to 46.3 ± 0.88%, respectively. From the result obtained, the study suggested that the wide range of the antioxidant activity may be due to the variety bio-active compounds present in the *C. fenestratum* extract.

In order to discover the bio-active compounds present in the *C. fenestratum* extract which contributed to the antioxidant property, other tests were carried out. The finding showed a large amount of total phenolic compounds exist in the *C. fenestratum* extract which were 18.35 ± 0.56 mg GAE/g in stem extract and 9.35 ± 0.67 mg GAE/g in leaf extract when tested with Folin-Ciocalteu method, using gallic acid as standard. Besides that, flavonoid test was also performed, and the result showed that high amount of flavonoids was present in the *C. fenestratum* stem extract with 12.8 ± 0.88 mg QE/; meanwhile in the leaf extract, the amount of flavonoid was only 3.2 ± 0.78 mg QE/g (Goveas and Abraham 2013). Another study by Neethu et al. (2014) presents the relationship between diabetic condition and the oxidative stress state. From their finding, oxidative stress was the mechanism underlying diabetes which results from the failure to maintain the radical generating and radical scavenging system in the balance mode. In the diabetic rats, the antioxidant activities of the major antioxidant enzymes such as glutathione-S-transferase and catalase in the liver were notably decreased. However, when the rats were treated with methanolic stem extract of *C. fenestratum*, the oxidant activity improved near

the normal range. Glutathione-S-transferase activity was increased from 0.0399 ± 0.07 to 0.1295 ± 0.002; meanwhile catalase activity was enhanced from 0.2485 ± 0.015 to 0.536 ± 0.0415 when treated with *C. fenestratum* extract. As a conclusion, *C. fenestratum* extract acts on the antioxidant enzymes to exert the antioxidant effect.

5.5.6 Antihypertensive and Vasorelaxant Activity

In vitro study conducted by Wongcome et al. (2007) showed that berberine extracted from the *C. fenestratum* was able to show hypotensive effect. The *C. fenestratum* was extracted with water in the same manner as traditional medicine practitioners usually do by boiling the dried stem of *C. fenestratum* in water. In the study, the aortic ring of the tested rat was first precontracted with phenylephrine (PE). PE is an alpha-adrenoreceptor agonist and exhibited vasocontraction effect by increasing K^+ uptake in the endothelium-intact aorta (Palacios et al. 2013) and induced the release of the Ca^{2+} from the calcium channel (Kim et al. 2014). Thus, precontracted aorta by PE was a simulated condition of the aorta in the hypertension state. When the extract of the *C. fenestratum* was tested on the PE-contracted rat aorta, the aorta starts to show a vasorelaxant effect. The relaxation effect of *C. fenestratum* was dose-dependent and achieved IC_{50} at the concentration of 20.89 μg/ml. Moreover, *C. fenestratum* extraction also showed relaxation effect even when the endothelium was removed (Wongcome et al. 2007). Thus, this study suggested that hypotensive effect of *C. fenestratum* extract was perhaps associated with the inhibition of Ca^{2+} immobilization.

Other than PE, Wongcome et al. (2007) also used potassium chloride (KCl) to generate vasoconstriction effect. KCl is a membrane-repolarizing agent which is capable of repolarizing the membrane to generate more action potential to produce more vasoconstriction effect (Wong 1996). The same procedure was repeated as the KCl-contracted rat aorta was tested with *C. fenestratum* extract to observe the relaxation effect. However, the relaxation effect of *C. fenestratum* extract was less when KCl acted as vasoconstrictor and the effect continued to diminish when endothelium was removed. This result may indicate the relationship between endothelium-derived relaxing factors and nitric oxide with *C. fenestratum* extract. Furthermore, when the endothelium-intact aorta was treated with L-N(ω)-nitro-arginine methyl ester (L-NAME), the vasorelaxant effect of the *C. fenestratum* extract was decreased since L-NAME is a nitric oxide synthase inhibitor. Hence, the finding proposed that *C. fenestratum* extract may stimulate endothelium-dependent relaxation by releasing nitric oxide. As a conclusion, *C. fenestratum* extract did show vasorelaxant effect in the isolated aortic rings precontracted with PE and KCl. The vasorelaxant activity may be diminished in the absence of endothelium and with the L-NAME treatment. The vasorelaxant activity of *C. fenestratum* also depends on nitric oxide which is an endothelium-derived releasing factor.

5.5.7 Antiulcer Activity

In the study conducted by Okechukwu et al. (2013), they discovered that *C. fenestratum* exhibit antiulcerative activity by using partially purified fraction (PPF) obtained from dichloromethane stem extract of *C. fenestratum*. It was used to treat against the risk factor of peptic ulcer disease which is prolonged use of non-steroidal anti-inflammatory drugs (NSAIDs). NSAIDs will interfere with the cyclooxygenase-1 pathway (COX) which in turn causes prostaglandin depletion. Prostaglandin is important for cytoprotection of the stomach as prostaglandin inhibits the secretion of gastric acid and prevents gastric bleeding caused by indomethacin (Robert 1984).

Other than that, stress can also induce peptic ulcer disease in the gastrointestinal tract. The pathogenesis of stress-induced ulcer is due to mucosal ischemia which can lead to the mucosa damaged by interfering with anion exchange (HCO_3^- for Cl^-), which will eventually disrupt the protective endothelium layer. Upon the disruption of the HCO_3^- protective layer, gastric acid may erode the epithelium layer and cause peptic ulcer disease (Silen et al. 1981). Hence, this study by Okechukwu et al. (2013) had found the treatment of peptic ulcer disease by using medicinal plant, *C. fenestratum*. The findings showed that PPF displayed a significant antiulcerative effect against peptic ulcer disease. They found that *C. fenestratum* extract was able to reduce the ulcerative lesion index in HCl/EtOH-induced gastric ulcer by 76.2%. Moreover, *C. fenestratum* also showed powerful effect in indomethacin-induced gastric ulcer by causing 74.60% ulcerative lesion index reduction. Meanwhile, the strongest *C. fenestratum* antiulcerative effect was displayed in the stress-induced gastric ulcer that showed the highest ulcerative lesion index reduction by 93.5% (Okechukwu et al. 2013). Hence, the finding from this study revealed that *C. fenestratum* was efficient in treating peptic ulcer diseases.

5.5.8 Neuroprotective and Cholinoprotective Activity

Chronic alcohol consumption was found to be the cause of neurodegeneration and cholinergic neuronal damage. In the study performed by the Phachonpai et al. (2012), they tested rats by ingesting ethanol via peritoneal for 14 days with dose of 1.8 g/kg. The brains of the rats were taken out and undergo several cell testing. Their findings found that ethanol-ingested rats notably showed less neuronal cell survival in both the hippocampus and cerebral cortex. The most susceptible region of the brain affected by ethanol was the dentate gyrus that is located at the hippocampus; meanwhile occipital cortex, a part of the cerebral cortex, was the least affected by the ethanol.

The action of ethanol in the brain tissues may be due to the activation of apoptosis from the disruption of mitochondrial membranes and cytochrome C release and consequently caused caspase-3 activation to start neuro-apoptosis processes (Young et al. 2003). Other than that, ethanol ingestion also may lead to oxidative stress to

the brain tissue which causes brain damage. The conversion of ethanol to acetaldehyde and acetate leads to the generation of the reactive oxygen species (ROS). The brain tissue contain a great amount of fatty acids and susceptible to undergo oxidation process, and during that time bio-active product (aldehyde) may induced neurodegenerative effect (Hernandez et al. 2016).

However, the degenerative brain tissue were reversed when prophylactic treatment with 5 mg kg^{-1} of *C. fenestratum* extract was given to the rats which portrayed markedly rise in the neuronal survival densities in almost all brain region except temporal cortex. Other than neuroprotective effect, *C. fenestratum* extract also showed cholinoprotective effect. Cholinergic neuron density in the hippocampus regions was also decreased when treated with ethanol, but when supplemented with *C. fenestratum* extract, the deterioration of the cholinergic neurons was decreased in all parts of the hippocampus except CA3 region (Phachonpai et al. 2012). Hence, *C. fenestratum* can be consumed as daily supplement to delay neurodegenerative effect that may occur later in the life process like Alzheimer's disease and Parkinson's disease. Last but not the least, alcohol consumption is harmful to the body, for instance, it can damage the brain.

5.5.9 Wound Healing Activity

In a study conducted by Anitha et al. (2011), they discovered the wound healing ability of *C. fenestratum* extract which was due to the flavonoid content present in the extract. The whole plant of *C. fenestratum* was air-dried and pulverized into fine powders and then undergone several extraction processes before formulating the compound into (oil-in-water) O/W cream. *C. fenestratum* cream was tested for its efficacy to treat the wound in excision and incision wound model. The rate of wound healing in *C. fenestratum* cream test group was faster than in the control group with mean period epithelisation of 10.15 ± 0.50 days compared to 15.46 ± 0.45 days. On the 16th day, the percentage of wound contraction was notably increased when *C. fenestratum* cream was applied. *C. fenestratum* cream demonstrates 75.1 ± 1.25% of wound contraction which is higher than the control group that exhibited 59.50 ± 1.14% wound contraction (Anitha et al. 2011). Thus, in this study, it is proven that *C. fenestratum* extract was efficient to enhance wound healing activity.

In another study carried out by Thangathirupathi and Bhuvaneswari (2011), they tested the albino rat's excision and incision model with povidone-iodine ointment (5% w/w) as standard wound healing agent with *C. fenestratum* extract ointment. They found that *C. fenestratum* ethanolic extract ointment at 5% and 10%w/w concentrations assist in the wound healing process by increasing the tensile strength in the incision wound model. When 5% w/w extract and 10% w/w *C. fenestratum* extract were tested in the excision model, the result was consistent with the wound healing effect of povidone-iodine (5% w/w) (Thangathirupathi and Bhuvaneswari 2011). Hence, the wound healing effect of *C. fenestratum* extract is almost similar to the effect of already well-established drug to treat the wound.

5.6 Clinical Study of Berberine

Zeng et al. (2003) conducted a study to assess the efficacy of berberine in the treatment of chronic congestive heart failure (CHF). One hundred and fifty-six patients with CHF were assigned into this test, where 79 patients were orally treated with 1.2–2.0 g/day of berberine, while the other 77 patients were treated with placebo, and the results were evaluated after 8 weeks of treatment. In comparison with placebo-treated patients, berberine-treated patients had higher improvement in the 6 min walking (exercise capacity) test and left ventricular ejection fraction (LVEF) (pumps oxygenated blood to the rest of the body) and a decrease in the ventricular premature complexes (VPC) (extra heartbeats) and non-sustained ventricular tachycardia (VT) (marker of increased risk for sudden cardiac death). Besides that, long-term effect of berberine treatment gave no apparent side effects and reduced mortality, thus improving the quality of life in patients with CHF. Exercise capacity was improved due to some possible reasons. First, it may be due to the increase in the function of LV or together with the decreased in blood pressure. Second, improvement in the exercise capacity might be attributed by the α-adrenergic receptor and central sympathetic effect to maintain homeostasis (Benfey 1982; Greco 1983; Wang 1998).

The potential of berberine as cholesterol-lowering drug was studied by Kong et al. (2004). Oral administration of berberine was conducted to 32 hypercholesterolemia patients who are receiving no other drugs, herbs, or diets before treatment with berberine. In the study, the patients received 0.5 g of berberine twice per day for 3 months. Positive effects were proven with the reduction of serum cholesterol by 29%, triglycerides (TG) by 35% and low-density lipoprotein (LDL) cholesterol by 25%. The cholesterol-lowering effect of berberine is due to the increased expression and half-life of the low-density lipoprotein receptor (LDLR) on the hepatocyte surface, which consequently stabilized mRNA.

Yin et al. (2008) conducted a pilot study at outpatient department of Xinhua Hospital to test the efficacy of the berberine (isolated from *Coptis chinensis French*). Thirty-six adults diagnosed with type 2 diabetes were tested in random which received 1500 mg/day of berberine or metformin for a period of 3 months. From the study, they stated that monotherapy of berberine notably decreased glycated haemoglobin (HbA_{1C}), FBG and postprandial blood glucose (PBG), and the effect was as good as metformin which was widely used as hypoglycaemic agent. However, berberine was more efficacious than metformin in reducing serum triglyceride and cholesterol level although the decrease did not achieve statistical significance. The combination therapy of berberine with other hypoglycaemic agents showed that berberine was competent to enhance insulin sensitivity which was reported that approximately 50% of HOMA-IR value was reduced. This finding was important as the treatment of type 2 diabetes mellitus. They also found that the waist/hip ratio (WHR) of the patient was decreased without significant decrease in their body weight that may be because of distribution of fat by berberine. Furthermore, the combination of berberine and insulin showed that both fasting and postprandial C-peptides increased significantly. Then, they also proposed that long-term berberine treatment may improve insulin secretion in diabetic patients (Yin et al. 2008).

Zhang et al. (2008) also conducted a clinical test to 116 patients with type 2 diabetes also associated with dyslipidaemia which received oral treatment with 1.0 g/day of berberine for 3 months, and the effectiveness of berberine was compared with placebo. The effectiveness of berberine was shown from the reduction of fasting and post-load plasma glucose, HbA_{1c}, TG, total cholesterol (TC) and LDL-C and increase of glucose disposal rate. In another study, Affuso et al. (2010) conducted a randomized clinical test to 50 mild hypercholesterolemia insulin-resistant patients for 6 weeks of treatment with combination of 500 mg berberine, 200 mg red yeast rice and 10 mg policosanols. The effect of this nutraceutical combination was compared with the treatment of placebo alone. Here, berberine positive effects were proven through the decrease of TC, LDLC and TG levels, endothelial-dependent flow-mediated dilation (FMD) and insulin sensitivity from the arm of patients receiving nutraceutical combination treatment. Affuso et al. (2012) conducted another study to 59 patients with metabolic syndrome, and similar positive effect of berberine on insulin-resistance was improved with orally treatment of nutraceutical combination consisting berberine, red yeast rice and policosanol.

On the other hand, blood glucose-lowering effect of berberine was tested by Zhang et al. (2010) against patients with diabetes type 2 mellitus at Nanjing First Hospital. In the study, 50 patients were orally assigned with berberine with dose 1 g/day, 26 patients were orally assigned with metformin with dose 1.5 g/day and 21 patients were also orally assigned with rosiglitazone with dose 4 mg/day, where the test was conducted for 2 months. From the results, berberine reduced fasting blood glucose (FBG) by 25.9%, HbA_{1c} by 18.1% and TG by 17.6%. Here, the lowering efficacies were almost similar with metformin and rosiglitazone. However, berberine has a higher effect on the reduction of TG. Moreover, the positive results were demonstrated by patients with hepatitis B and C, which show its safety use by patients with liver function damage. As explained by Turner et al. (2008), the glucose-lowering effect is due to the reduction in level of peroxisome proliferator-activated receptor-Y, preadipocyte differentiation and lipid droplet accumulation.

The lipid-lowering effect of berberine was also further studied by Dong et al. (2012) who reviewed 2 meta-analyses of trials in the treatment of type 2 diabetes mellitus involving 1068 participants with dose between 0.5 and 1.5 g/day ranging from 8 to 24 weeks. Generally, a similar pattern was observed with the reduction on plasma levels of TG, TC and LDL, with significant increase of plasma HDL cholesterol concentration upon treatment with berberine. Furthermore, Dong et al. (2012) concluded that berberine has hypoglycaemic effect after being used in combination with antidiabetic agents and thus is able to reduce blood sugar level.

Synergistic effect of berberine with other nutraceutical agents and simvastatin was studied by Cicero et al. (2007) and Kong et al. (2008), where the therapy combination of berberine improved the efficacy of berberine in inhibiting cholesterol synthesis and lipid lowering, respectively. Cicero et al. (2007) carried out the study to 40 randomized patients with moderate dyslipidaemias which were orally administered with 500 mg/day of berberine, 10 mg/day of policosanol and 3 mg/day of red yeast extract for 4 weeks. Here, the reduction of TG (26%), LDL-C (25%), TC (20%) and apolipoprotein B (ApoB) (29%) was higher in combination treatment

compared to the treatment of 500 mg/day berberine alone, with lower reduction of TG (22%), LDL-C (20%), TC (16%) and ApoB (15%). In addition, Kong et al. conducted a test to 63 outpatients diagnosed with hypercholesterolemia, which were divided into three groups. First, second and third group received 1 g/day of berberine, 20 mg/day of simvastatin and combination of berberine and simvastatin, respectively, for 2 months. Surprisingly, combination treatment reduced 31.8% of serum LDC-C and 38.9% of TG, which are higher than monotherapies, indicating that anti-lipid effect has been improved.

The beneficial effects of berberine on endothelium were studied by Xu et al. (2008) and Xu et al. (2009). Xu et al. first conducted a test to 15 healthy volunteers to study the mobilization of endothelial cells. The study proved that the mobilization of circulating endothelial progenitor cells (EPC) with CD34/KDR double positivity in small arteries was increased significantly upon receiving 400 mg thrice a day of berberine for a month. Second, Xu et al. conducted a test to 20 healthy volunteers, which also received 400 mg thrice a day of berberine for a month. Here, berberine enhanced production of nitric acid, and this induced the regulation and function of EPC including proliferation, adhesion and migration. In addition, Cheng et al. (2013) evaluated the effectiveness of berberine on endothelial function to 12 healthy subjects which received 0.4 g of berberine thrice a day for 1 month and compared with 11 healthy subjects that act as control. From the study, the levels of serum malondialdehyde (MDA) and synthesis of nitric oxide (NO) were significantly reduced, and reactive oxygen species (ROS) and NADPH oxide 4 (Nox4) protein expressions were facilitated. Here, berberine shows a partially reducing oxidative stress of vascular endothelium which contributes to the effectiveness of berberine in the amelioration of endothelial function and thus is able to treat atherosclerotic and coronary artery diseases.

Clinical tests of berberine show that berberine has significant effect in treating patients with type 2 diabetes, dyslipidaemia, hypercholesterolemia, congestive heart failure and atherosclerotic and coronary artery diseases.

5.7 Conclusion and Future Perspectives

The major biological active constituent of *C. fenestratum* is berberine which exhibits several pharmacological effects such as antidiabetic, anticancer, antibacterial and antimalarial. Meanwhile, phenolic compounds and flavonoids of *C. fenestratum* are responsible for antioxidant activities and wound healing effect. Moreover, *C. fenestratum* extract also can manage hypertension, peptic ulcer and neurodegenerative effect. Hence, *C. fenestratum* is proven to be effective in the treatment of those diseases. Based on its various pharmaceutical activities, it is recommended to establish clinical setting on the development of *C. fenestratum* for the treatment of diabetes in particular, based on berberine as an active principle. Studies on pharmacokinetics, toxicity and underlying mechanism of action of berberine need to be conducted. This information is to highlight the fact that berberine is a potential compound present in this plant for future pharmaceutical formulations. Establishment

of the metabolic profiling using the latest spectroscopic technology is also becoming an opportunity for future study. Necessary action have to be taken to protect the species from being critically endangered and from exploitation (Sarvalingam and Rajendran 2016).

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