

Chapter 3.31

Orthosiphon stamineus (Java Tea)

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HISTORICAL NOTE

Orthosiphon stamineus (vernacular name: barbiflore, Java tea, misai kucing, kabling-gubat, kumis kucing, cat's whiskers, kidney tea, rau meo, remujung, balbas pusa, moustaches de chat, and yaa nuat maeo; synonym: *Clerodendranthus spicatus*, *Ocimum aristatum*, *Orthosiphon aristatus*, *Orthosiphon grandiflorus*, *Orthosiphon spicatus*, *Orthosiphonis folium*) has long been used in traditional medicine in East India, Indo China, South East Asia, and tropical regions of Australia where the plant is usually found. *O. stamineus* belongs to the Lamiaceae family and is a perennial herb. The stem is four-angled reaching a height ranging from 0.3 to 1 m, and the flowers are white or pale lilac. The flower has stamens (>2 cm) extending from the corolla tube. The leaves are about 2–4 cm wide and 4–7 cm long and have a lanceolate-like, elliptical, or rhomboid shape. The aerial parts (dried stem and leaves) are commonly brewed as a tea for a variety of purposes, from treating inflammatory disorders to ailments of the urogenital tract. This plant is commonly used in South East Asian folk medicine for diabetes, hypertension, gallstone, tonsillitis, epilepsy, rheumatoid diseases, menstrual disorder, gonorrhoea, syphilis, renal calculus, lithiasis, edema, eruptive fever, influenza, hepatitis, and jaundice. However, scientific studies on the medicinal benefits of *O. stamineus* do not confirm all its traditional uses. Nevertheless, *O. stamineus* is well known for its potent diuretic effect, which is stronger than other natural diuretics (Burkill, 1966).

CHEMICAL COMPONENTS

Chemical compounds extracted from *O. stamineus* leaves vary greatly with the type of solvent used and the auxiliary energy the process is subjected to. Major compounds often found from *O. stamineus* extracts are rosmarinic acid, eupatorin, and sinensetin. In fact, these compounds are often used to standardize products derived from this plant. Extraction using water often produced a lower yield of flavonoids (i.e., sinensetin, eupatorin, eupatorin-5-methyl ether) due to the lower solubility of flavonoids in water (Pang et al., 2017). Extraction using pure organic solvents such as ethanol and isopropanol yielded the highest concentration of flavonoids (methoxylated compounds), but a very low concentration of rosmarinic acid (hydroxylated compounds). The presence of excessive energy during the extraction process may induce thermal degradation of polyphenolic compounds (Pang et al., 2014) and may produce danshenshu (Nuengchamng et al., 2011) and caffeic acid. Extracts from *O. stamineus* were found to contain essential oil fragments, diterpenes, phenolic acid, and flavonoids. In addition, *O. stamineus* extract was found to be rich in potassium (Basheer and Majid, 2010). The full list of compounds found in *O. stamineus* is listed in Table 3.31.1.

TRADITIONAL USE

The diuretic effect of *O. stamineus* leaf extract has long been well known in the South East Asian community. Owing to such a benefit, decoctions of *O. stamineus* have been used in folk medicine for treatment of various kidney diseases from infection to renal calculi. Normally, urinary tract infection is treated with a decoction of fresh leaves taken twice a day, despite there being no systematic knowledge on the dosage required for effective treatment. A decoction of dried leaves is often used for treatment of strangury and dysuria. The whole plant either dried or fresh is used to treat kidney stones by traditional medical practitioners (Muhlisah, 2007). The Filipinos also take a decoction of the leaves to relieve gout (De Padua et al., 1987). The Kenyah people of Sarawak, Malaysia, use the young twigs and leaves of *O. stamineus* for treatment of backache (Chai, 2006).

TABLE 3.31.1 Active Compounds From *Orthosiphon stamineus*

Type	Compounds	References
Phenolic acid	Danshensu Salvionolic acid B Cafaric acid Sagerinic acid	Nuengchamngong et al. (2011)
	Rosmarinic acid Caffeic acid Lithospermic acid Chicoric acid	Sumaryono et al. (1991)
Flavonoids	Ladanein Vomifoliol 7',3',4'-Tri-O-methyluteolin 6-Hydroxy-5,7,4'-trimethoxyflavone	Tezuka et al. (2000)
	Eupatorin Tetramethylscutellarein 5-Hydroxy-6,7,3',4'-tetramethoxyflavone 3'-Hydroxy-5,6,7,4'-tetramethoxyflavone Sinensetin Pillion Salvegenin Cirsimaritin Rhamnazin Apigenin trimethyl ether Luteolin tetramethyl ether	Malterud et al. (1989)
Essential oil fragments	β -Caryophyllene α -Humulene β -Elemene 1-Octen-3-ol β -Bourbonene β -Pinene Caryophyllene oxide Camphene Limonene α -Pinene 1,8-Cineol Borneol Linalool Camphor Eugenol p-Cymene Carvone Bornyl acetate δ -Cadinene	Hossain et al. (2008)
Diterpenes	Orthosiphols A–Z	Awale et al. (2001, 2002, 2003), Masuda et al. (1992), Nguyen et al. (2004), Stampoulis et al. (1999), Takeda et al. (1993) and Tezuka et al. (2000)
	Staminols A–D	Awale et al. (2003), Nguyen et al. (2004), Stampoulis et al. (1999) and Tezuka et al. (2000)
	Staminolactones A–B	Stampoulis et al. (1999) and Tezuka et al. (2000)
	Secoorthosiphols A–C	Awale et al. (2002) and Nguyen et al. (2004)
	Nororthosiphonolide A	Awale et al. (2002)
	Norstaminolactone A	Awale et al. (2002)

TABLE 3.31.1 Active Compounds From *Orthosiphon stamineus*—cont'd

Type	Compounds	References
	Norstaminols A–C	Awale et al. (2002, 2003), Stampoulis et al. (1999) and Tezuka et al. (2000)
	Norstaminone A	Awale et al. (2001)
	Neoorthosiphonone A	Awale et al. (2004)
	Neoorthosiphols A–B	Awale et al. (2001, 2003), Nguyen et al. (2004), Ohashi et al. (2000) and Shibuya et al. (1999)
	Siphonols A–E	Awale et al. (2003)
	Orthochromene A	Ohashi et al. (2000)
Triterpene	Ursolic acid Oleanolic acid Betulinic acid	Tezuka et al. (2000)
	Hydroxybetulinic acid Maslinic acid α -Amyrin β -Amyrin	Hossain and Ismail (2013)
Benzochromene	Methylripariochromene A	Guerin et al. (1989)

MAIN ACTIONS

Antidiabetic Activity

Extracts from *O. stamineus* have antidiabetic properties which are believed to be due to their interaction with glucose metabolism (i.e., both inhibiting and increasing glucose uptake by diaphragm muscles). This plant is also reported as a popular antidiabetic alternative medicine for type II diabetes.

A chloroform subfraction of *O. stamineus* leaves containing eupatorin (1.48%) and sinensetin (2.26%) was found to inhibit glucose uptake in streptozotocin-induced diabetic rats at an intestinal absorption rate of 500–2000 $\mu\text{g/mL}$, although the effect is no better than the reference drug metformin (Mohamed et al., 2013). Mohamed et al. (2012) showed that a 50% ethanolic extract of *O. stamineus* leaves inhibits α -glucosidase (IC_{50} of 4.63 mg/mL) and α -amylase (IC_{50} of 36.70 mg/mL), which they attributed to the presence of sinensetin. Sinensetin had an IC_{50} of 0.66 g/mL and maximum inhibition of 89% (2.5 mg/mL) for α -glucosidase and an IC_{50} of 1.13 mg/mL and maximum inhibition of 85.8% (2.5 mg/mL) for α -amylase. Thus, the plant extract inhibits the process of converting carbohydrates to glucose and hence helps regulate glucose levels in diabetic patients. They stated that sinensetin outperformed the reference drug acarbose. Earlier, Sriplang et al. (2007) reported up to 35% reduction of blood glucose in streptozotocin-induced diabetic rats using 1000 mg/kg of *O. stamineus* water extract. They noted an effect comparable with that of the reference drug glibenclamide. Blood glucose reduction is not caused by sinensetin alone because the water extract usually has an almost undetectable amount of sinensetin (Pang et al., 2017). The fact that water extract is responsible for blood glucose reduction according to Sriplang et al. (2007) means water-soluble compounds other than sinensetin must be responsible for the same actions. Elucidation of these compounds still awaits further investigation.

Water extract does not stimulate insulin secretion when tested in vitro (Sriplang et al., 2007). Similarly, a chloroform subfraction of plant leaves containing eupatorin at 1.48% and sinensetin at 2.26% also fails to stimulate insulin secretion in diabetic rats at doses up to 1000 mg/kg for 2 weeks (Mohamed et al., 2013), although it was found to suppress insulin release in response to subcutaneous glucose load (Mohamed et al., 2011a) and oral glucose test (Sriplang et al., 2007).

O. stamineus extract has also been found to stimulate glycogen synthesis. Mohamed et al. (2013) reported that chloroform extract containing 1.48% eupatorin and 2.26% sinensetin increased glucose uptake by diaphragm muscles at a rate of 2 mg/mL in a different way from that of insulin, despite not being effective at a lower concentration (i.e., 0.5–1 mg/mL). It is possible that *O. stamineus* stimulates glucose uptake into muscle cells, even though it is not known whether this applies to the largest body of muscle (i.e., skeletal muscle).

Mohamed et al. (2013) reported that a chloroform subfraction of plant leaves could reduce blood glucose level in streptozotocin-induced diabetic rats. The dose ranged from 500 to 1000 mg/kg taken orally twice daily for 14 days. They noted potency was significantly less than the reference drug metformin at 500 mg/kg. *O. stamineus* water extract also yielded a 13% reduction in fasting blood glucose for a similar dose and duration (Sriplang et al., 2007). In terms of percentage reduction in fasting blood glucose a dose of 1000 mg/kg had a similar effect to that of the reference drug glibenclamide, but the glucose concentration of the latter was slightly lower. According to Mohamed et al. (2011b) the extract could reduce blood glucose in a subcutaneous glucose tolerance test without inducing hypoglycemia, which suggests that the mechanism of action is related to 5'-AMP-activated protein kinase (AMPK). *O. stamineus* plant extract has the potential to reduce blood glucose levels in diabetic subjects.

Diuretic Activity

O. stamineus water extract increased urine output in Sprague-Dawley rats and the diuretic activity was dose dependent (Adam et al., 2009). The diuretic effect was lower than those of furosemide and hydrochlorothiazide, the medicine often used for diuresis. They observed higher than normal urinary potassium excretion and elevated blood urea nitrogen, creatinine, and glucose levels, but all remained within the normal range. Methanol–water extract of *O. stamineus* leaves showed diuretic effects comparable with those of hydrochlorothiazide for both acute and chronic administration (Arafat et al., 2008). They reported a reduction in uric acid level after 6 h in much the same way as occurs with allopurinol for hyperuricemic rats.

The diuretic effect of *O. stamineus* extract is attributed to the presence of methoxy flavonoids (i.e., sinensetin and tetramethylscutellarein) which have an antagonistic effect on adenosine receptors (Yuliana et al., 2009). Thus, the diuretic properties of *O. stamineus* are due to the affinity of its active compounds to adenosine receptor ligands.

Nephroprotective Activity: Kidney Stone Treatment

Zhong et al. (2012) reported that *O. stamineus* extracts can reduce the synthesis of calcium-based stones in the kidneys. In their work calcium oxalate induced nephrolithiasis in rats fed with 80–160 mg/kg of *O. stamineus* extract. They used the phenolic, flavonoid, and polysaccharide content derived from the main *O. stamineus* extracts for the test. They observed that urinary calcium and oxalate excretion increased and that the effect was dose dependent. They concluded the polysaccharide extracts of *O. stamineus* provided the most significant reduction of CaOx crystal nucleation and aggregation. Rodgers et al. (2014) reported that *O. stamineus* water extract reduced the growth rate of calcium oxalate in much the same way as Cystone, although Cystone was more effective (30.9%) than *O. stamineus* water extract (20%) in reducing overall CaOx crystal size.

Premgamone et al. (2001) evaluated the effect of drinking *O. stamineus* tea made from 2.5 g of sun-dried plant material on 48 renal calculi subjects split into 2 groups for 18 months. They compared the effect with that of the reference drug (i.e., 5–10 g granular sodium potassium citrate). They found a significant reduction in kidney stone size for both study groups at an annual rate of $28.6 \pm 16.0\%$ and $33.8 \pm 23.6\%$ for *O. stamineus* and sodium potassium citrate, respectively. At the end of treatment, 90% of initial clinical symptoms (i.e., back pain, headaches, and joint pain) were relieved. No side effects were reported from subjects with *O. stamineus*; however, fatigue and loss of appetite were observed in 26.3% of subjects treated with sodium potassium citrate. Currently, there is no evidence that the plant extract is more potent than the currently used drug. However, the plant has the potential to reduce calcium-based stones production in the kidneys with no side effects.

Antihypertensive Activity

A chloroform subfraction of *O. stamineus* extract containing methylripariochromene A was shown to reduce blood pressure in spontaneously hypertensive rats (Matsubara et al., 1999). Manshor et al. (2013) reported that 50% methanolic extract and water extract of *O. stamineus* at a dose of 1000 mg/kg can also reduce blood pressure in spontaneously hypertensive rats. It is not clear whether methylripariochromene A was present in the extract, since quantification of the compound was not reported. The greatest effect was found with the methanolic extract, but it was still less than that of the reference drug losartan.

In a random clinical study of 80 subjects, Cicero et al. (2012) reported a mild but notable reduction in systolic, diastolic, and pulse pressure in hypertensive dyslipidemic subjects treated with a nutraceutical containing *O. stamineus* for 8 weeks. They reported no significant difference in cardiovascular disease risk at the end of the trial. The antihypertensive effect of *O. stamineus* is notable, although less potent than that of the reference drug hydrochlorothiazide. Elsewhere, Trimarco et al. (2012) showed a significant reduction in mean 24-hour systolic and diastolic blood pressure levels compared with baseline

values for subjects treated with supplements containing *O. stamineus* from their clinical trial involving 27 subjects. In contrast, the subjects treated with a supplement containing a combination of policosanol, red yeast rice extract, berberine, folic acid, and coenzyme Q10 (without *O. stamineus*) showed no significant reduction in blood pressure. Earlier, [Supari \(2002\)](#) reported systolic and diastolic blood pressure equivalent to amlodipine in mild and moderate hypertensive subjects taking a mixture supplement of *Apium graveolens* and *O. stamineus*.

Hepatoprotective Activity

[Yam et al. \(2007\)](#) observed the hepatoprotective effect of *O. stamineus* 50% aqueous methanolic extracts on CCl₄-induced rats. They monitored normalization of the liver rate function using alanine transaminase and aspartate transaminase as indicators. They found the effect was dose dependent and that it was only effective at higher doses (i.e., >250 mg/kg). [Alshawsh et al. \(2011\)](#) studied the hepatoprotective effect that a 95% ethanolic extract of *O. stamineus* given at rates of 100 and 200 mg/kg daily for 2 months had on thioacetamide-induced liver cirrhosis in rats. They found the hepatoprotective effect was dose dependent and that it was only significant at the higher dose (i.e., 200 mg/kg). They suggested the hepatoprotective effect was due to neutralization of the toxic compounds through the cytochrome p450 pathway. Nevertheless, the hepatoprotective effect was less potent than the reference drug silymarin (50 mg/kg) which comes from milk thistle. All these studies show that *O. stamineus* extract possesses hepatoprotective properties, although clinical trials on humans are not available.

Gastroprotective Activity

[Yam et al. \(2009\)](#) studied the antiulcerogenic activity of *O. stamineus* methanolic extract using an ethanol-induced gastric ulcer rat model. They reported a marked histological improvement in the healing of mucosal damage in groups receiving *O. stamineus* methanolic extracts. They concluded the gastroprotective effects of *O. stamineus* extract were due to its ability to inhibit lipid peroxidation and stimulate gastric mucus secretion.

Antiproliferative Properties and Cancer Treatment

O. stamineus contains diterpenes and flavonoids that display mild antiproliferative properties against liver metastatic colon 26-L5 carcinoma and human HT1080 fibrosarcoma cell lines ([Awale et al., 2001, 2002](#)). *O. stamineus* ethanolic extract was found to suppress HCT116 colorectal tumors in mice ([Ahamed et al., 2012](#)). The latter authors' in vitro test shows that *O. stamineus* is noncytotoxic to colon cancer and endothelial cells, but it appears to suppress vascular endothelial growth factor. The anticancer properties of *O. stamineus* lack clinical evidence, and more studies are needed to further understand its efficacy.

TOXICITY

The LD₅₀ of *O. stamineus* is estimated to be greater than 5000 mg/kg with no apparent toxicity reported in Sprague-Dawley rats after 14 days. Despite a benign increase in liver weight and a reduction in serum enzymes ([Chin et al., 2008](#)) and despite the absence of toxicity at this dose being reproduced acutely ([Abdullah et al., 2009](#)) and subchronically over a period of 28 days with 50% ethanolic extract ([Mohamed et al., 2011a](#)), *O. stamineus* water extract showed no genotoxic effects in *Salmonella* and doses up to 4000 mg/kg showed no genotoxic effects in a mouse bone marrow test ([Muhammad et al., 2011](#)). *O. stamineus* extract is neither toxic nor genotoxic with tested doses five to ten times higher than effective supplemented doses.

ADVERSE EFFECTS AND INTERACTIONS WITH DRUGS

In most clinical studies, pregnant or lactating women, persons with liver or heart failure, and persons who have had a stroke are often excluded for safety reasons due to limited information available on interaction with *O. stamineus*. Caution should be observed in patients with hypertensive therapy when taking *O. stamineus* because there is a possibility of bringing about an orthostatic hypotensive attack ([Globinmed, 2017](#)). [Garcia-Moran et al. \(2004\)](#) wrote a letter to *Gastroenterology and Hepatology* complaining about potential development of acute hepatitis as a result of consuming *O. stamineus* tea; however, this claim has yet to be substantiated elsewhere. Moreover, *O. stamineus* is consumed widely as herbal tea in South East Asia without any reported complaint related to hepatitis.

O. stamineus-based supplements should not be taken with other diuretics because such a combination may cause hypertension and congestive cardiac failure. In the presence of cardiac and renal insufficiency, caution is advised when taking this supplement. Adam et al. (2009) noted that there is a risk of hypoglycemia when *O. stamineus* is taken together with antidiabetic drugs.

CONCLUSIONS

It is clear from reviewing preclinical and clinical trials on *O. stamineus* that the plant shows significant promise as diuretic, antidiabetic, antihypertensive, nephroprotective, hepatoprotective, gastroprotective, antiproliferative and anticancer drug. The effective dose of the plant extract ranging from 200 to 1000 mg/kg is not toxic with the LD₅₀ estimated to be greater than 5000 mg/kg. At present, how it interacts with other drugs is not yet fully understood. However, as a precaution it is recommended that *O. stamineus*-based supplements should not be taken in conjunction with other diuresis or hypertensive therapy.

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