Indonesian Journal of Science and Education
Volume 3, Number 1, April 2019, pp: 26 ~ 33
p-ISSN: 2598-5213, e-ISSN: 2598-5205, DOI: 10.31002/ijose.v3i1.729
e-mail: ijose@untidar.ac.id, website: jurnal.untidar.ac.id/index.php/ijose

Orthosiphon stamineus Benth (Uses and Bioactivities)

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Received: April 24th, 2018 *Revised: October 23th, 2018* *Accepted: April 11th, 2019*

ABSTRACT

Orthosiphon stamineus Benth., or *kumis kucing* is a the medicinal plants have been used as diuretic medicine. The utilization of medicinal plants associated to its secondary metabolite. This article aims to explain uses pf the *O. stamineus* and the its secondary metabolites. This article is based on literature offline and online media. Offline literature used the books, whereas online media used Web, Scopus, Pubmed, and scientific journals. *Orthosiphon stamineus* has two varieties called purple varieties (which have purple-colored flowers) and white varieties (which have white-colored flowers). Some of secondary metabolites in the *O. stamineus* are the terpenoids, phenols, isopimaran type ispenimoids, flavonoids, benzochromes, and organic acid derivatives. The traditional medicine of the *Orthosiphon stamineus* uses as the diuretic, hypertension, hepatitis, jaundice, and diabetes mellitus.

Keywords: *Orthosiphon stamineus, diuretics, diterpenoids, hypertension*

INTRODUCTION

Orthosiphon stamineus Benth is a species belonging of the Lamiaceae, that by Indonesia local communities known *kumis kucing* (cat's whiskers). The name of a cat's whiskers was related to the its flower structure, which has the stamens structure like to the cat's whiskers. Lamiaceae have about 200 genera and 3200 species (Congruist, 1981). The Lamiaceae have 8 major genera i.e: *Salvia* (500 species), *Hyptis* (350 species), *Scutellaria* (200 species), *Coleus* (200 species), *Plectranthus* (200 species), *Stachys* (200 species), Nepeta (150 species), and *Teucrium* (100 species) (Congruist, 1981).

The *O. stamineus* by local communities in Indonesia have been usedas diuretic or urinary remedy and to cure diabetes mellitus (Achmad *et al*., 2008). The *O. stamineus* also used as an ornamental plant because its have an flower structure attractive and have tight branching pattern, so that its suitable uses living fence. Those resulted the *O. stamineus* easily found in yards.

Based on the structure of flowers, *O. stamineus* is grouped into two varieties namely purple varieties (purple colored flowers) and white varieties (white colored flowers). The both varieties of *O. stamineus* contain varies bioactive compounds, whereas the purple varieties have higher bioactive content than the white varieties (Lee, 2004). In general the *O. stamineus* produces compounds such as terpenoids and phenols (isopimaran, flavonoid, benzochromen) and organic acid derivatives. The characteristic of the dihydpenoid is isolated from *O. staminieus* have an isopimuric carbon skeleton comprising three rings and contain many oxygen functional groups on C-1, 2, 3, and 7 carbon atoms.

The secondary metabolites plants associated to efficacy as drugs which uses as traditional medicine and modern medicine. In traditional medicine the cat whiskers are used as diuretic, and to cure the diabetes mellitus (Achmad *et al*., 2008),

anti hypertension (Manshor *et al*., 2013), but discussion has not been done extensively. This article will be one of the sources of information on the relationship of utilization and the content of bioactive compounds from the cat whiskers plant.

RESEARCH METHODS

This paper is based on literature review both online and offline. Offline is based on literature books such as and other books. Online media is based on Web, Scopus, Pubmed, and on-line media used for the publication of Scientific journals.

DISCUSSION

BOTANY OF *Orthosiphon stamineus* Benth

Orthosiphon stamineus Benth sinonim with *Orthosiphon aristatus* (Bl.) Miq., *Orthosiphon grandiflorus* Bold., *Orthosiphon spicatus* (Jempol) Bak. is a species belonging of the *Lamiaceae*. Vernaculer name of the *O. stamineus* such as *misai kucing* (Malaysia), *kumis kucing* (Indonesia), and java tea (Europe), is native in South East Asian (Indubala and Ng, 2000). The Benth Orthosiphon genus consists of 40 species spread across tropical and subtropical Asia including South Africa and Madagascar (Sadashiva *et al*., 2013). The genera *Orthosiphon* is derived from two ortho words (straight), while siphon (tube or cylindrical). Both words when combined mean a straight tube like a flower produced by species in the genus *Orthosiphon*. The characteristic of this straight tube is considered to be one of the main characteristics of the Labiatae or Lamiaceae family (Keng and Siong, 2006). Some species in the genus *Orthosiphon* are used as medicaments such as *O. aristatus*, *O. pallidus*, *O. thymiflorus*, *O. stamineus* especially in traditional medicine to prevent it different diseases such as diabetes mellitus, kidney stones, edema, rheumatism, hepatitis, hypertension and jaundice (Singh *et al*., 2015).

Keng and Siong (2006) states that *O. stamineus* has two varieties based on its flower color, purple variety and white varieties. The purple variety has higher bioactive content than the white varieties (Lee, 2004), however in different lighting sometimes the color of both varieties is difficult to distinguish. Orthosiphon stamineus can grow about 1.2 m and its leaves can be harvested within 2-3 months after planting (Abdullah *et al*., 2012).

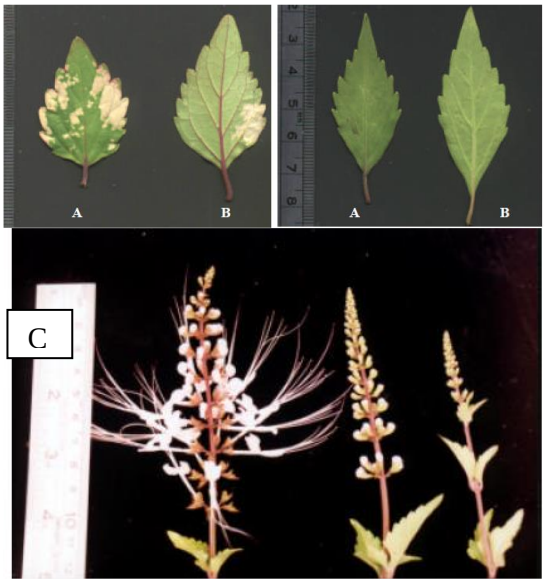


Figure 1. Differences of leaves morphological structure of *O. stamineus* (A) top surface and (B) bottom surface. Left over purple varieties while upper right of white varieties, (C) flowering (Keng and Siong 2006).

The two varieties of cats whiskers are morphologically difficult to distinguish (Keng and Siong, 2006), but when viewed more detai there are differences in the morphology of leaves and flowers. The color of the bones of the leaves and flowers shows its varieties, so that the whiskers plant of purple flowering cats are called purple varieties and the white flowering ones are called white varieties. The purple variety has an ovate shaped leaf shape and a purple leaf vein, and yellowish spots are spreaded unevenly on the lower surface as well as the top surface of the leaves. White varieties have a rhomboid leaf shape with no spot, a obtuse-like basal section, while the apex is acuminate, with a bright green

colored vein (Figure 1). The most striking difference in the two varieties of cat's whiskers is the color of the petals and the crown of flowers. The purple variety has a lobe color on both lips of bright purple corolla lips while white varieties have maroon color. Leaf microstructure, anther, stigma and pollen grains are the same in both varieties (Keng and Siong, 2006).

THE USES OF THE *O. stamineus*

World health organization (WHO) stated that 80% of people living in developing countries generally use traditional medicine to maintain their health. Utilization of plants as ingredients in both the form of crude extracts and simplicia increasing, associated with the tendency of back to nature. This resulted in the documentation and research of medicinal plants as a drug increasingly, especially in the tropics such as Indonesia. The research objectives varies are documenting of the local knowledge of tribe (ethnomedicine), isolation of bioactivity compounds, bioassays, and bioprospection.

Orthosiphon stamineus has long been used either as a traditional medicine or herbal medicine. The empirically of local people uses the cats whiskers as medicine of kidney disease. Nevertheless, studies have shown more widespread cats whiskers, such as hypertension (Manshor *et al*., 2013), hepatitis, jaundice (Alshawsh *et al*., 2011), and diabetes mellitus (Mohamed *et al*. 2013; Amer et al 2015).

Anti Diabetes Mellitus

Diabetes mellitus or also known as diabetes is the metabolic disolder which characterized by decreased secretion and / or insulin resistance (Munin and Hanani 2011). Diabetes mellitus is global threat, which ranks fourth cause of non-communicable disease death after cardio vascular disease, cancer, and respiratory diseases (Schwarz *et al.*, 2013). By 2014 an estimated 387 million people are identified as diabetics worldwide (IDF, 2014), and about 80% are represented by low and middle-income countries (IDF, 2014; Wild *et al*., 2004).

The diabetes mellitus caused by disolder of glucose metabolism in the blood does not work well so that blood sugar levels are higher than normal conditions (hyperglycemia). Anti-hyperglycemic agents are agents that can lower blood glucose levels but do not go beyond fasting levels, whereas hypoglycemic agents are compounds capable of reducing blood glucose levels to below fasting levels. Metformin compound is a commercial anti-hyperglycemic agent while glibenclamide is a hypoglycemic agent (Mohamed *et al*., 2013). Glibenclamide acts by stimulating insulin release from pancreatic β cells (Mariam *et al*., 1996). Another action that may cause hypoglycemic effects of glibenclamide is the suppression of glucagons release (Joel and Lee, 2001). In normal circumstances fasting glucose <100mg / dL and glucose levels after 2 hours of eating <140mg / dL. In people with diabetes mellitua blood glucose> 126 mg / dL or glucose> 200 mg / dL at 2 hours after eating (Munin and Hanani, 2011).

Plants that can be used as drug diabetes mellitus is plant that maintain blood glucose levels at normal levels. Provision of oral leaves extract of oral plants of 1 g/kg, in mice able to reduce normal glucose levels of mice below the level of fasting concentration (Mariam *et al*., 1996). The mechanisms of herbal medicine in controlling blood glucose levels are (1) inhibiting the hydrolysis of carbohydrates into glucose in the gastrointestinal tract, resulting in reduced amount of glucose absorbed into the blood; (2) inhibition of sugar formation in the liver; and (3) increase insulin secretion and its sensitivity and increase glucose uptake (Munin and Hanani, 2011).

Empirically, local people usually use plants that have a bitter taste as a drug diabetes mellitus including the plant of cat whiskers (*O. stamineus*). The leaves of *O. stamineus* have been reported to have hypoglycemic and anti hypperglycemic activity (Mariam et al., 1995). Mohamed *et*

al. (2013) stated that the fraction of chloroform extract from *O. stamineus* was able to inhibit the increase of blood glucose level in mice that had been given streptozotosin. Giving chloroform extract of *O. stamineus* leaves at a dose of 1 g/kg twice daily in diabetic rats for 14 days showed a significant decrease (Mohamed *et al*., 2013). Azam *et al*. (2017) states that the extract of the cat's whiskers leaves can stabilize the blood sugar of rats treated with streptozotocin, its ability comparable to 10 mg/kg bw of glibenclamide (commercial antidiabetes). Systematic metabolic pathway analysis identifies that water extracts from *O. stamineus* contribute to antidiabetic activity mainly through the regulation of the tricarboxylic acid cycle, glycolysis/ gluconeogenesis, lipid and amino acid metabolism (Azam *et al*., 2017).

Sinensetin is identified in the leaves of *O. stamines* (Hossain and Ismail, 2016). Hyperglycemia will induce glucotoxicity in pancreatic β cells, resulting in poor deterioration of insulin secretion and glycemic control. The hexane extract of *O. stamineus* increased the expression of insulin mRNA as well as pancreatic and duodenal homeobox-1 from INS-1 cells by dose dependent. The hexane extract of *O. stamineus* increased the expression of insulin mRNA and prevented induced glucotoxicity by 3 days treatment (Lee *et al*., 2015).

Antioxdants

Reactive oxygen species (ROS) and other free radicals are responsible for many diseases, such as arteriosclerosis, heart disease, aging, and cancer (Willcox *et al*., 2004). Free radicals such as ROS, including hydroxyl radicals, superoxide anions, and hydrogen peroxide, play an important role in increasing the destruction of living tissues. The antioxidant activity of phenolic compounds is found mainly because it inhibits its redox through neutralization and free radical cooling (Galato *et al*., 2001).

The radical scavenging method of 2,20-diphenyl-1-picrylhydrazyl (DPPH) is a frequently used method for the determination of antioxidant activity. Water extract from O. stamineus showed significant free radical scavenging activity of IC50 9.6 μg /mL, while IC50 for ethanol extract was 21.4 μg/mL. Methanol extract from O. stratus showed good anti oxidant super oxide, anti radical hydroxyl, ferrous chelating ion, and antilipid peroxidation activity (Yam *et al*., 2012). Administration of methanol extract from O. stratus at concentrations of 1250, 2500, and 5000 mg / kg / day for 28 days showed no signs of acute toxicity. Furthermore, there were no significant differences in body weight, relative organ weight, and hematologic and biochemical parameters between female and female mice in the tested dose. No organ abnormalities were observed between both treatment and control groups (Yam *et al*., 2012).

Hepatitis

The liver is an important organ responsible for metabolism, bile secretion, substance elimination, blood detoxification, synthesis, and important hormonal regulation. *Orthosiphon stamineus* has long been exploited by local Malaysians in the treatment of hepatitis and jaundice (Alshawsh *et al*., 2011). Paracetamol is a commercial chemical compound used to reduce fever, but its usage has a negative impact on liver damage. Paracetamol (2 g / kg) has increased SGOT, SGPT, ALP and lipid peroxide in the liver, but administration of methanol extract of O. stamineus leaves (200mg / kg) restores normal properties in the liver, so *O. stamineus* has hepatoprotective activity. The ethanol extract from *O. stamineus* has been studied to determine the hepatoprotective effect in rats induced by thioacetamide (Alshawsh *et al*., 2011).

Antimicrobial

Antimicrobial compounds are compounds that inhibit microbial growth such as microscopic fungi and bacteria. A total of 72 isolates of endophytic fungi were isolated from the various organs of the cat's whiskers plant as many as 48 isolates from

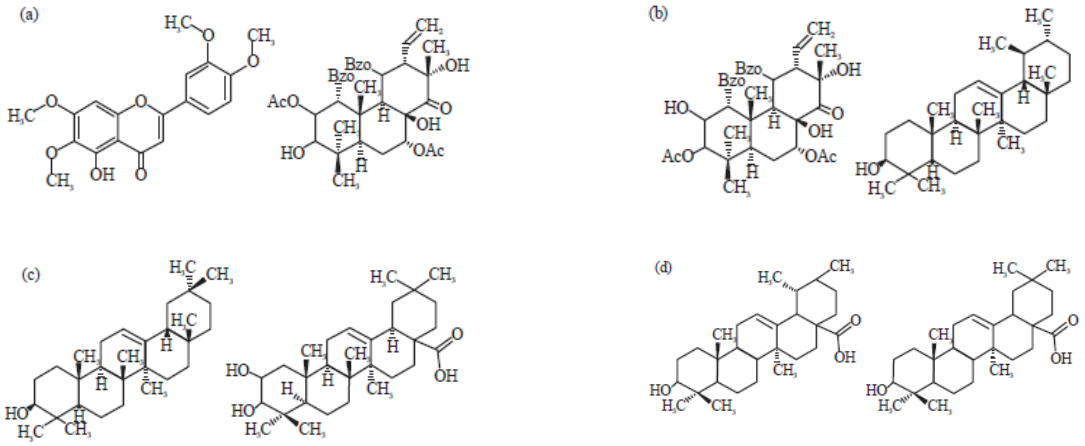
the leaves, 14 isolates from the stem, 6 isolates from the roots and 4 isolates from the flower and 92% had activity as anti microbial (Tong *et al*., 2011). The anti-bacterial properties were investigated by disc diffusion method and minimum inhibitory of concentration (MIC) against four strains of bacteria (Gram-positive and Gram-negative) (Alshawsh *et al*., 2012). The best antimicrobial activity was demonstrated by the *O. staminus* water extract against *Staphylococcus aureus*, with a 10.5 mm inhibition zone and a MIC value of 1.56 mg / mL (Alshawsh *et al*., 2012).

SECONDARY METABILITES

Secondary metabolites are compounds used by humans for the purposes of treatment, insecticides, dyes, perfumes, and spices. Plants synthesize of secondary metabolites use to defenses in unfavorable environments, therefore their content varies between plant species, growth periods, and environmental types. This resulted in secondary metabolites of plants are very diverse types and is estimated to reach 10,000 species.

Orthosiphon produces various types of secondary metabolites, which is used as a drug ingredient. In general, secondary metabolites in plants are distinguished into phenolic, terpenoid and alkaloid compounds (Taiz and Zeiger, 2006), which can then be divided into smaller groups. *Orthosiphon stamineus* contains active phenolic compounds such as flavonoids (Almatar *et al*., 2013). Other studies revealed different things that the chloroform fraction of boiled water leaves the cat whiskers containing isopimaran type dihydrogen compounds. Cat whiskers contain percentages of sinensetin, eupatorin, and 30-hydroxy-5,6,7,40-tetrametoksiflavon in chloroform extracts are 1.48%, 2.26% and 0.58%, respectively (Mohamed et al., 2013). Leaf extract of *O. stamineus* contains three flavonoids (30-hydroxy-5,6,7,40-tetrametoksiflavon, sinensetin, and eupatorin) as bioactive substances (Yam *et al*., 2012).

Various types of chemical compounds that have been isolated from *Orthosiphon* species include monoterpenes, diterpenes, triterpenes, saponins, organic acids and flavonoid compounds (Singh *et al*., 2015) (Figure 2). The methanol extract showed the presence of phenolic and flavanoid compounds. Six flavonoid compounds were isolated from the leaves of the medicinal plant *O. stamineus*. Based on chemical and spectral analyzes, the structures are described as eupatorin, sinensetin, 5-hydroxy-6,7,30,40-tetrametoxiflavone, salvigenin, 6-hydroxy-5,7,40-trimethoxyflavone and 5,6,7,30-tetramethoxy -40-hydroxy-8-Cprenylflavone (Hossain and Rahman, 2015).



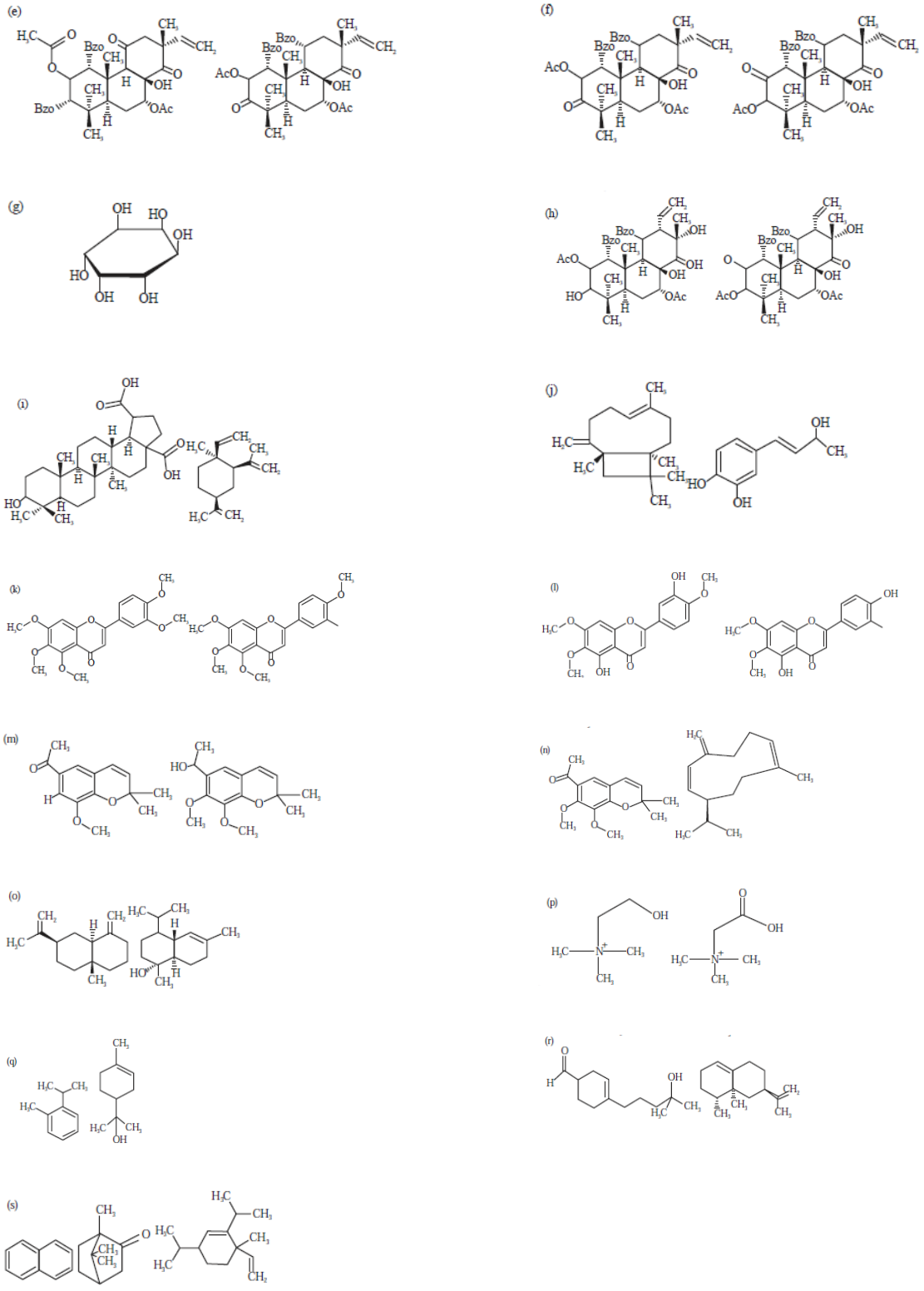


Figure 2. The chemical structure of typical and bioactive compounds isolated from *Orthosiphon* yaitu: (a) 3'-hydroxy-5,6,7,4'-tetramethoxyflavone neoorthosiphol A, (b) neoorthosiphol B α-amyrin, (c) β-amyrin maslinic acid, (d) urosolic acid oleanolicv acid, (e) orthosiphonone A orthosiphonone B, (f) orthosiphol A orthosiphol B, (g) myo-inositol, (h) neoorthosiphol A neoorthosiphol B, (i) betulinic acid β-elemene, (j) β-caryophyllene caffeic acid, (k) sinensetin tetra-methyl scutellarein, (l) eupatorin cirsimaritin, (m) acetovanillochromene orthochromene A, (n) methylripario chromene agermacrene-D, (o) β-selinen α-cadinol, (p) choline betaine, (q) O-cyamenea-terpineol, (r) lyrol valencene, dan (s) nephthalin camphor α-elemene (Singh et al 2015).

CONCLUSIONS

Orthosiphon stamineus have two varieties called purple varieties (purple colored flowers) and white varieties (white colored flowers). *Orthosiphon stamineus* produces terpenoid compounds and phenol compounds such as isopimaran, flavonoid, benzochromen, and organic acid derivatives. In traditional medicine *O. stamineus* are used as diuretic, hypertension, hepatitis, jaundice, and diabetes mellitus.

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