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Review Article

FROM ETHNOPHARMACOLOGY TO CLINICAL STUDY OF *ORTHOSIPHON STAMINEUS* BENTH.

I KETUT ADNYANA, FINNA SETIAWAN, MUHAMAD INSANU

School Of Pharmacy, Institute Technology Bandung, Jalan Ganesa 10, Bandung 40132, Indonesia. Email : insanu@fa.itb.ac.id

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ABSTRACT

Extensive research has been carried out on *Orthosiphon stamineus* Benth. (lamiaceae) since the 1930s. This plant is used in several countries (especially in Indonesia, Malaysia, Thailand, Vietnam and Myanmar) as traditional medicine. From its ethnobotanical uses the plant is known for several activities. Because of those reasons, *O. stamineus* is potential to be developed as a new source of drugs. This report comprehensively reviews ethnopharmacological, isolated chemical compounds, pharmacological, toxicological and clinical studies of *O. stamineus.* Electronic databases (e.g., Pubmed, Scopus, academic journals, Elsevier, Springerlink) were used for searches. Web searches were attempted using Google applying *Orthosiphon stamineus,* java tea, antihypertensive, sinensetin, methylripariochromene A as keywords. Phytochemical studies reported about 116 compounds that isolated from this plant classified as monoterpenes, diterpenes, triterpenes, saponins, flavonoids, essential oil and organic acids. Pharmacological studies for whole extract, tincture, selected fraction or pure compounds isolated from this plant showed antioxidant, antitumor, diuretic and nephroprotective, antidiabetic, antihypertensive, antiinflammation, antimicrobial, antiobesity and hepatoprotective. Traditional use of *O. stamineus* meets its scientific evidence in aspects of phytochemical, pharmacological, toxicological as well as clinical.

Keywords : Kumis kucing, Java tea, Antihypertensive, Sinensetin, Methylripariochromene A

INTRODUCTION

Indonesian traditional medicine (jamu, Javanese traditional medicine; usada, Balinese traditional medicine; Madura's formula) have been widely used as conventional medicine in many areas of Indonesia. Since 2005, these natural medicines were divided into three categories. The classifications were empirical traditional medicine (jamu), standardized herbal medicine (obat herbal terstandar) and phytopharmaceutical (fitofarmaka). The differences between these categories were based on their requirements. Jamu could be marketed only based on empirical data or people experiences but the herbal standardized medicine (obat herbal standar) should be based on pharmacological and toxicological studies on animal, its raw materials should be standardized. The phytopharmaceutical (fitofarmaka) product was the highest rank, because it could be marketed only after preclinical and clinical studies [1, 2].

Orthosphon stamineus is a perennial herb. It attains 0.3-1.5 m high and having 4-angle stem. Leaves are simple, opposite, ovate-oblong-lanceolate, elliptic or rhamboid, which have 2-4 cm wide and 4-7 cm long. The flowers are white, blue or violet. When the flowers open, stamens and pistil extend out far beyond the petals, which create "cat's whiskers" effect. This plant needs full sun and a moist garden soil for growing and flowering. However, it grows perfectly under light shade and warmer climates [3, 4].

Kumis kucing is belong to Lamiacae or Labiatae family, the synonyms are *O. aristatus* (Blume) Miq., *O. longiflorum* Ham., *O. grandiflorum et aristatum* Bl., *O. spiralis* Merr., *O. grandiflorus* Bold. *Clerodendranthus spicatus* (Thumb.) C.Y.Wu ex H.W.Li., and *Trichostemma spiralis* Lour. This plant is also known for various local names, they are kutum, mamam, bunga laba-laba, remuk jung, remujung, kumis ucing, songot koceng, sesalaseyan (Java), java tea, cat's whisker, Indian kidney tea (English), mao xu cao (China), misai kucing, ruku hutan (malaysia), kabling gubat, kabling parang (Philippine), se-cho, myit-shwe (Myanmar), rau-meo (Vietnam), neko no hige (Japan), katzenbart (Germany) and yaa-nuad-maew, pa-yab-mek (Thailand) [3-6].

Ethnopharmacological Studies

Kumis kucing is used in several South East Asian countries especially in Indonesia, Malaysia, Thailand, Vietnam and Myanmar. It is found in extending area from tropical Asia to tropical Australia. It is wild but can be planted. This plant has been traditionally used for many diseases. *O. Stamineus* is also recognized in European country, such as Holland, France and England to be consumed as a herbal product.

In Indonesia, this plant is under systemic cultivation. The leaves have been used for diuretic, preventing and treating rheumatism, diabetes mellitus, hypertension, tonsillitis, epilepsy, menstrual disorder, gonorrhoea, syphilis, renal calculi, gallstone, acute and chronic nephritis, gout arthritis, and antipyretic. [4-6].

In Vietnam, the aerial part is used for treating urinary lithiasis, edema, eruptive fever, influenza, hepatitis, jaundice and biliary lithiasis. In Malaysia, the leaves are used for diuretic and treating catarrh of the bladder. A decoction prepared from the plant can be used to eliminate stones in the bladder. In Myanmar, the leaves are reported as an antidiabetic, while decoction of the air dried leaves can be used to treat urinary tract and renal diseases. In Thailand, the leaves are used for diuretic, kidney tonic, and cystotonic medicines. In Okinawa Prefecture, Japan, this plant is systemically cultivated and consumed as a healthy Java tea to facilitate body detoxification [3].

Chemical constituents

The phytochemical study of kumis kucing grown in Asia have been conducted extensively since the 1930's. More than hundreds chemical compounds were reported and classified as monoterpenes, diterpenes, triterpenes, saponins, flavonoids, organic acids, and etc (**Table 1** and **Figure 1**).

Moreover, previous research have detected 69 chemical compounds in the essential oil of leaves of *O. Stamineus.* They were β-Carryophyllene, α-Humulene, β-Elemene, 1-Octen-3-ol, β-Bourbene, β-Pinene, Phenylacetaldehyde, Caryophyllene oxide, Camphene, cis-2-Octenal, 3-Octanol, Limonene, 2-Pentenyl furane, Hexanal, Naphtalene, Benzaldehyde, trans 2-Hexanal, Heptenal, trans cis-Octa-3-5-dien-2-one, Decanal, δ-Elemene, 1,8-Cineol, 4-Heptenal, Isomenthone, Methylchavicol, α-Pinene,Tridecan, ρ-Cymene, Camphor, 1-Methylnaphtalene, α-Muniolene, trans trans-Octa-3-5-dien-2-one, 2-Amylfurane, Menthone, Carvone, Cittonellol, α-Copaene, Borneol, Dodecane, Eugenol, Linalool, trans-Linalooloxide, δ-Cadipene, trans-2-(cis)-6- Nonadienale, Methyleugenol, α-Gubebene, Geranylacetane, δ-Terpineol, Acetophenone, trans- Anethol, Germacrene D, β-Cyclocitral, Damascenone, Dehydroionone, cis-Linalooloxide, Undecan, Bornyl Acetate, 2-Methylnapthalene, β-Ionone, Perillen, Safranal, Hexahydrofamesylacetone,Hexan-1-ol,2,6,6-Trimethyl-2-cyclohexe-1,4-dione, Isobornylacetate, trans, trans-Deca-2,4-dienal, cis-Caryophylene, Germacrene, and cis-3-Hexen-1-ol [7].

Pharmacological activities

Pharmacological studies of *O. stamineus* have been determined for whole extract, tincture, selected fraction and pure compounds. They

showed antioxidant, antitumor, diuretic, antidiabetic, antihypertensive, antiinflammation, antibacterial, and hepatoprotective activities.

Cardiovascular system

Administration of 1.0 and 5.0% infusion in a dose of 1.0 ml/kg increased cardiac contraction amplitude. Those accelerated atrioventricular and intraventricular conductivity as well as the entire ventricular complex [42].

Antioxidant

Various kinds of extracts of *O. stamineus* (distilled water, 50% aqueous methanol, methanol, 70% aqueous acetone and chloroform extracts) have been tested for free radical-scavenging activity, using a 1,1-diphenyl-2-picrylhydrazyl *invitro* model system. The highest activity was found in acetone extract. Other report observed that there were variations in total phenolic compunds, ranging from 6.7 to 10.1 mg caffeic acid/g dry weight of the methanol extract. This showed its antioxidative potency was comparable with quercetin and butylated hydroxylanisole (BHA) [32]. They also proved using different *in vitro* method (superoxide scavenging and xanthine oxidase) that *O. stamineus* extract showed potential antioxidant activity. [11, 32-34]. More than fifty compounds were isolated from *O. Stamineus*. They were tested their antioxidant activity using inhibition of NO production in LPS-activated machropage-like J774.1 cells. Siphonol A – C and E, 2-*O*-deacethylorthosiphol J, orthosiphol A, B, D, H, K, M, N, O, X, Y staminol A, neoorthosiphol B, Staminols C and D, orthosiphonones C and D and 14-deoxo-14-*O*-acetylorthosiphol Y, nororthosiphonolide A, orthosiphonone A, secoorthosiphols B and C and 3-*O*-deacetylorthosiphol I showed stronger antioxidative activity than NG-monomethyl-L-arginine as positive control. 2-*O*-deacetylorthosiphonone A showed the most potent activity, with an IC_{50} value of 35.0 μM. They proposed a structure-activity relationship of these diterpenes on the inhibition of NO production [9, 10, 12, 17, 23, 25]. Free radical scavenging activity of 5,7,4′-trimethylapigenin, eupatorin and 5,7,3′,4′-tetramethylluteolin were tested on enzyme-stabilizing effect. 15-lipoxygenase was used for that test. These compounds decreased enzyme-stabilizing effects by 50% at concentrations of 2.0 ± 0.04, 2.4 ± 0.3 and 4.3 ± 1.1 μM, respectively. Moreover, it was reported that the enzyme was inactivated by air bubbling and lost of sulfhydryl groups [15].

Cytotoxic

Norstaminolactone A, orthosiphols A, B, D, E, K, L, M, N, O, P and Q, nororthosiphonolide A, orthosiphonone A, norstaminone A and neoorthosiphol A were tested for their cytotoxic activities against highly liver metastatic colon 26-L5 carcinoma and human HT-1080 cell lines. The results showed that almost all compounds displayed weak to mild antiproliferative activities. Only norstaminolactone A showed a potent antiproliferative activities with IC_{50} value of 2.16 mg/ml against highly liver metastatic colon 26-L5 carcinoma cell line [13, 24, 27, 28, 30, 35]

Diuretic and Nephroprotective

Diuretic activity of hydroalcohol extract from aerial parts of *O. stamineus* was reported. At a dose of 50 mg/kg, this extract showed similar effect with hydrochlorotiazide at a dose of 10 mg/kg [36]. Other studies reported that an aqueous extract and leaves tincture enhanced ion excretion of rats which were not due to the potassium content of the starting material [37]. Nephroprotective effect of methanol extract was observed using gentamycin-induced nephrotic model in rats. Administration of methanol extract at doses of 100 and 200 mg/kg bw significantly decreased serum creatinine levels, blood urea, urinary protein and extent renal damage after 10 days administration [38].

Table 1: Phytochemical compounds present in *Orthosiphon stamineus* Benth.

No	Chemical compounds	Source	References
1	1-octen-3-ol	Aerial part	[7]
2	2,3-dicaffeoyltartaric acid	Aerial part	[8]
3	2-*O*-deacetylorthosiphol J	Aerial part	[9, 10]
4	3-hydroxy-5,6,7,4'-tetramethoxyflavone	Aerial part	[11]
5	3-*O*-deacetylorthosiphol I	Aerial part	[9, 12]
6	4'-hydroxy-5,6,7-trimethoxyflavone	Aerial part	[13]
7	4',5,6,7-tetramethoxyflavone	Aerial part	[14]
8	5,6-dihydroxy-7,4'-dimethoxyflavone	Aerial part	[14]
9	5,7,4'-Trimethylapigenin	Aerial part	[15]
10	5,6,7,4'-tetramethoxyflavone	Aerial part	[16]
11	5,7,3',4'-tetramethylluteolin	Aerial part	[15]
12	5-hydroxy-6,7,3',4'-tetramethoxyflavone	Aerial part	[13]
13	6-hydroxyorthosiphol B	Aerial part	[9, 10]
14	6-hydroxy-5,7,4'-trimethoxyflavone	Aerial part	[13]
15	7,3',4'-tri-*O*-methylluteolin	Aerial part	[13]
16	7-*O*-deacetylorthosiphol B	Aerial part	[9, 10]
17	14-deoxo-14-O-acetylorthosiphol Y	Aerial part	[17]
18	α –cadinol	Aerial part	[18]
19	α-humulene	Aerial part	[7]
20	β-bourbonene	Aerial part	[7]
21	β –caryophyllene	Aerial part	[7]
22	β-elemene	Aerial part	[7]
23	β-pinene	Aerial part	[7]
24	β **–**sitosterol	Aerial part	[13]
25	β –carryophylene	Aerial part	[7]
26	β -hydroxybetulinic acid	Aerial part	[19]
27	Ɣ-cadinene	Aerial part	[7]
28	Acetovanillchromene	Aerial part	[20]
29	Aurantiamide acetate	Aerial part	[13]
30	Betulinic acid	Aerial part	[13]
31	Borneol	Aerial part	[7]
32	Bornyl acetate	Aerial part	[7]
33	Caffeic Acid	Aerial part	[8]
34	Caffeic acid depside A	Aerial part	[21]
35	Caffeic acid depside B	Aerial part	[21]
36	Caffeic acid depside C	Aerial part	[21]
37	Camphene	Aerial part	[7]
38	Camphor	Aerial part	[7]
39	Carotol	Aerial part	[18]
40	Carvone	Aerial part	[7]

41	Cis-Caryophyllene	Aerial part	[18]
42	Caryophyllene oxide	Aerial part	[7]
43	Cichoric acid	Aerial part	[21]
44	Cisimaritin	Aerial part	[13]
45	Eugenol	Aerial part	[7]
46	Eupatorin	Aerial part	[15]
47	Hederagenin	Aerial part	[13]
48	Ladanein	Aerial part	[13]
49	Limonene	Aerial part	[7]
50	Luteolin	Aerial part	[14]
51	Methylripariochromene A	Aerial part	[20]
52	Neoorthosiphol A	Aerial part	[22]
53	Neoorthosiphol B	Aerial part	[22]
54	Neoorthosiphone A	Aerial part	[23]
55	Norstaminol A	Aerial part	[13]
56	Norstaminol B	Aerial part	[24]
57	Norstaminol C	Aerial part	[24]
58	Norstaminolactone A	Aerial part	[24]
59	Nororthosiphonolide A	Aerial part	[25]
60	Norstaminone A	Aerial part	[25]
61	Oleanolic acid	Aerial part	[13]
62	Orthochromene A	Aerial part	[20]
63	Orthosiphol A	Aerial part	[26]
64	Orthosiphol B	Aerial part	[26]
65	Orthosiphol C	Aerial part	[10]
66	Orthosiphol D	Aerial part	[16]
67	Orthosiphol E	Aerial part	[16]
68	Orthosiphol F	Aerial part	[27]
69	Orthosiphol G	Aerial part	[27]
70	Orthosiphol H	Aerial part	[27]
71	Orthosiphol I	Aerial part	[27]
72	Orthosiphol J	Aerial part	[13]
73	Orthosiphol K	Aerial part	[28]
74	Orthosiphol L	Aerial part	[28]
75	Orthosiphol M	Aerial part	[28]
76	Orthosiphol N	Aerial part	[28]
77	Orthosiphol O	Aerial part	[28]
78	Orthosiphol P	Aerial part	[28]
79	Orthosiphol Q	Aerial part	[28]
80	Orthosiphol R	Aerial part	[24]
81	Orthosiphol S	Aerial part	[24]
82	Orthosiphol T	Aerial part	[24]
83	Orthosiphol U	Aerial part	[10]
84	Orthosiphol V	Aerial part	[10]
85	Orthosiphol W	Aerial part	[10]
86	Orthosiphol X	Aerial part	[10]
87	Orthosiphol Y	Aerial part	[10]
88	Orthosiphol Z	Aerial part	[10]
89	Orthosiphonone A	Aerial part	[25]
90	Orthosiphonone B	Aerial part	[29]
91	Orthosiphonone C	Aerial part	[17]
92	Orthosiphonone D	Aerial part	[17]
93	Pillion	Aerial part	[14]
94	Quercetin	Aerial part	[14]
95	Rosmarinic acid	Aerial part	[8]
96	Salvigenin	Aerial part	[13]
97	Secoorthosiphol A	Aerial part	[30]
98	Secoorthosiphol B	Aerial part	[30]
99	Secoorthosiphol C	Aerial part	[30]
100	Sinensetin	Aerial part	[13]
101	Siphonol A	Aerial part	[9]
102	Siphonol B	Aerial part	[9]
103	Siphonol C	Aerial part	[9]
104	Siphonol D	Aerial part	[9]
105	Siphonol E	Aerial part	[9]
106	Staminol A	Aerial part	[27]
107	Staminol B	Aerial part	[13]
108	Staminol C	Aerial part	[17]
109	Staminol D	Aerial part	[17]
110	Staminolactone A	Aerial part	[13]
111	Staminolactone B	Aerial part	[13]
112	Tetramethylscutellarine	Aerial part	[15]
113	Trans-ozic acid	Aerial part	[31]
114	Ursolic acid	Aerial part	[13]
115	Vomifoliol	Aerial part	[13]
116	16□-hydroxy betulinic acid	Aerial part	[19]

Antidiabetic

In oral glucose tolerance test, the water extract at doses of 0.2–1.0 g/kg significantly decreased plasma glucose concentration in dose-dependent manner for both normal and diabetic rats. At a dose of 1.0 g/kg showed similar effect with glibenclamide (5 mg/kg). In diabetic rats, after they were given the extract orally (0.5 g/kg) for 14 days, plasma glucose concentrations were reduced significantly. In addition, plasma triglyceride concentration was also lower in the extract-treated diabetic rats than that of untreated group. Furthermore, plasma HDL-cholesterol concentration was significantly increased in diabetic rats treated with the extract. In perfused rat pancreas, 100 µg/ml extract potentiated the glucose-induced insulin secretion [39]. Other study showed antidiabetic effects of the petroleum, chloroform, methanol and water extracts. Chloroform extract at a dose of 1 g/kg bw significantly reduced blood glucose level. Further, this extract was fractionated and finally one subfraction showed similar antidiabetic effect with metformin [40].

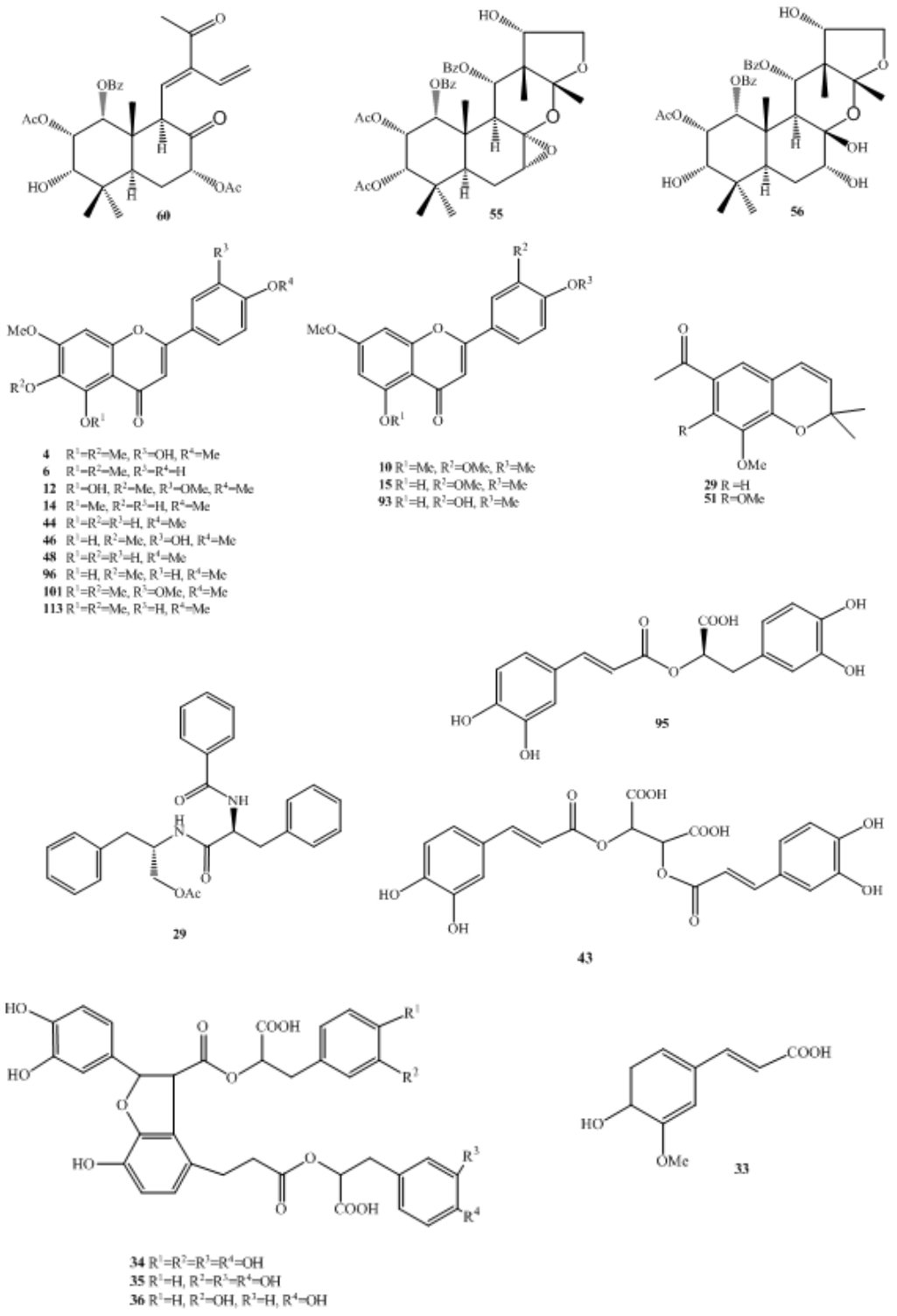

Fig. 1: Various compounds identified in *O. stamineus*

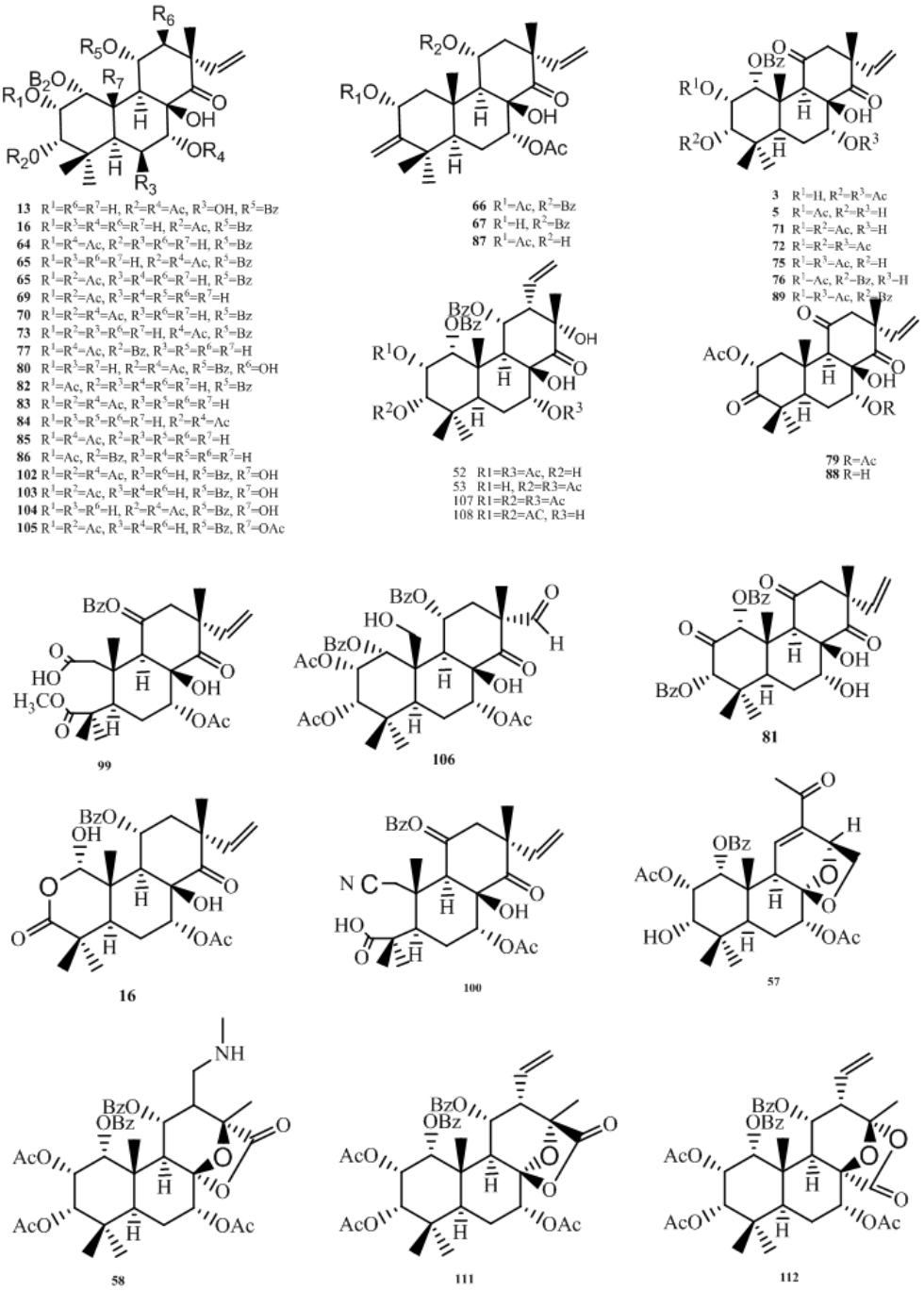

Fig. 1: Continued

Antihypertensive

Methylripariochromene A was isolated from the leaves of *O. Stamineus.* It had diuretic action and able to decrease blood pressure and cardiac output [20]. Moreover, it was reported that chloroform fraction from water decoction showed an inhibitory effect on the contractile responses on rat thoracic aorta smooth muscle stimulated with KCl beforehand. The chloroform fraction was then separated to afford orthochromene A, orthosiphonone A, orthosiphonone B and neoorthosiphol A, neoorthosiphol B, and methylripariochromene A. The compounds were tested for their anti-hypertensive activity. It was found that a major constituent in the water decoction of leaves decreased systolic blood pressure after subcutaneous administration in conscious stroke-prone spontaneously hypertensive rats (SHRSP) [41]. Methylripariochromene A, acetovanillochromene, orthochromene A, orthosiphonol A, B, orthosiphonone A, B showed their inhibitory actions for high K+-induced contractile responses in rat thoracic aorta by IC_{50} values of 2.19, 2.35, $3.47x10^{-5}$, 3.33, 2.86, 2.49, and $2.62x10^{-6}$ g/m, respectively. The dose dependent relaxation of aorta muscle contraction was stimulated by approximately 70 mM K^+ and decreasing in endocellular Ca^{2+} concentration were observed in methylripariochromene A at concentrations of 10^{-5}-10^{-4} g/mL. This effect was similar with nifedipine at $3x10^{-7}$-10^{-6} M. Moreover, antihypertensive activities of methylriparichoromene A, neoorthosiphol A and B, orthosiphol A, tetramethylscutellarein,

sinensetin, 5-hydroxy-6,7,3',4'-tetramethoxyflavone, eupatorin and orthosiphonone A and B were observed. The results showed that urinary volume was dose-dependently and it increased after oral administration of methylriparichoromene A, but the urinary concentrations of each electrolyte of Na+, K+ and Cl- were different with control group. The urinary excretion of these electrolytes were increased approximately two until three times in total, while tetramethylscutellarein, sinensetin and neoorthosiphol A and B showed remarkable relaxation on the contraction induced by 60 mM K+ or l-phenylephrine. Both orthosiphol A and orthosiphonone A showed significant suppressions in the vasocontraction. It was concluded that Antihypertensive actions of kumis kucing were caused by complex pharmacological mechanism from various kind of constituents such as flavones and isopimarane-type compounds due to diuretic action of methylriparichoromene A [20].

Antiinflammation

Subfraction of crude chloroform extract was active in inhibiting carrageenan-induced hind paw edema in mice. Moreover, orthosiphol A and B showed potent inhibitory activity against inflammation induced by TPA (12-*O*-tetradecanoylphorbol-13-acetate) one of tumor promoter [26].

Antimicrobial

Extract of *O. stamineus* showed antibacterial activity on serotypes c and d of *Streptococcus mutans* (MIC = 7.8–23.4 mg/ml). In the presence of 5% sucrose, the potency decreased about one-half for type d but no change was found in type c [43]. Methanol extract at concentration of 50% inhibited *Bacillus subtilis, Bacillus cereus, Staphylococcus aureus, Litseria monocytogenes, Escherichia coli, Vibrio parahaemolyticus, Salmonella enteritidis, Salmonella typhimurium,* and *Klebsiella pneumoniae* [7]. It was also proposed that antibacterial activities of *O. stamineus* due to the high concentration of rosmarinic acid.

Antiobesity

Administration of *O. stamineus* extract for two weeks significantly decreased total food intake, weight gain and visceral fat deposition in the Otsuka Long-Evans Tokushima Fatty (OLTF) rats. It was also found that leptin mRNA and proopiomelanocortin (POMC) expression increased but neuropeptide Y (NPY) expression decreased significantly compared to saline-treated group. It was concluded that the decreasing of food intake was followed by body weight and visceral fat mass reductions. Decreasing of food intake was associated with the increasing of hypothalamic POMC expression while decreasing NPY expression was caused by elevation of plasma leptin level [44].

Hepatoprotective

Pretreatment with *O. stamineus* extract at doses of 125, 250, 500 and 1000 mg/kg reduced the necrotic changes in rat liver and inhibited the elevation of serum alanine transaminase and aspartate transaminase levels. It was concluded that hepatoprotective effectwas caused by antioxidant and free radical scavenging properties [45]. Another study reported that methanol extract of leaves at a dose of 200 mg/kg showed hepatoprotective activity on paracetamol-induced rats. Futher, they proposed that these properties were due to the ability to prevent the depletion of the tissue GSH level [46]. Water extract of *O. stamineus* lowered bilirubin level in jaundiced rat. This was because of the increasing activity of glucoronyl transferrase that facilitated hepatic conjugation of billirubin or increased billirubin binding by albumin [47].

Toxicological studies

Acute toxicity of decoction was conducted. No toxicity was found at a dose of 2000 mg/kg [48]. It was reported that standardized 50% ethanol extract at a dose of 5000 mg/kg given orally to Sprague-Dawley (SD) female rats did not show any abnormalities in macroscopic and microscopic findings. These results were followed by subchronic toxicity. Extract administration at doses of 1250, 2500 and 5000 mg/kg on male and female SD rats for 28 days showed no signifincat differences with control group. The parameters were body weight, organ weights, haematological parameters, biochemistry values, macroscopic and microscopic observation of the brain, heart, liver, thymus, spleen, kidney, adrenal gland, lungs, testis, ovay, uterus, stomach or gut organs [49]. Chronic toxicity of water extract were also reported. High doses (0.96, 2.4 or 4.8 g/kg/day) reduced serum sodium level but increased alkaline phosphatase level. The incidence of hydrocalyx in male rats proposed that using high dose of this extract should be avoided [50].

Clinical studies

Clinical studies of kumis kucing were conducted as a single or combined with other plant extract. A phase II clinical study of fitofarmaka product (consist of a combination of *O. stamineus* and *Apium graviolens)* were done in "Jantung Harapan Kita" Hospital, Jakarta Indonesia. There were 160 patients with high blood pressure. All subjects were divided into two groups and they were administered the test product at a dose of 250 mg three times per day.The second group was treated with amlodipin (a calcium antagonist) as a standard at a dose of 5 mg five times per day. After 12 weeks treatment, the systolic and diastolic blood pressure were similarly decreased. Plasma electrolyte, lipid, blood glucose levels, and liver function were not influenced by the test product administration. Headache and nausea were occurred as adverse effects in both groups. One case of unstable angina was reported at first group but it was able to recover using nitrate treatment [51]. Another clinical study was on the efficacy of this plant and sodium potassium citrate in renal calculi treatment. Forty-eight farmers were recruited and randomly assigned to two groups. For a period up to 18 months, first group (group I) received 2 cups of *O. stamineus* tea daily, each tea cup was made from *O. stamineus* tea bag (contained 2.5 g dry weight), and second group (group II) received 5-10 g of granular sodium potassium citrate in solution divided into three times a day. Once every 5 to 7 weeks, subjects were interviewed, given additional drug supply, administered a kidney ultrasound and urine samples were collected for relevant biochemical analysis. From ultrasound images, rates of stone size reduction per year (ROSRPY) were calculated. The mean ROSRPY was 28.6 + 16.0% and 33.8 + 23.6% for group I and group II, respectively. These two means were not significantly different. Dissolution of stones was least in Level B (ROSRPY < mean - 0.5 SD) which was related to higher excretions of Ca and uric acid in the urine. After treatment, 90% of initial clinical symptoms (i.e. back pain, headaches and joint pain) were relieved. Fatigue and loss of appetite were observed in 26.3% of sodium potassium citrate treated subjects [52].

Conclusion & perspective

Orthosiphon stamineus Benth. is an Indonesian medicinal plant and growing well in many countries, especially Southeast Asia countries. This plant has a great potential value for cultivation because it contains secondary metabolites with interesting biological activities. About 116 compounds have been isolated from this plant. Some experiments have been conducted in the past for validating pharmacological uses of it, because *O. stamineus* was known for traditional use for treating some health problems which were cardiovascular, urinary, liver and metabolism disorder. Methylpariochromene A isolated from the leaves had diuretic action. It decreased blood pressure and cardiac output. 2-O-deacetylorthosiphonone A showed antioxidative property that inhibited NO production in LPS-activated machropage-like J774.1 cells. 5,7,4'-trimethylapigenin, eupatorin and 5,7',3',4'-tetramethylluteolin decreased enzyme stabilizing effects of 15-lipooxigenase. This action was due to air bubbling and lost of sulfhydryl groups. Norstaminolactone A was active against highly liver metastatic colon 26-L5 carcinoma cell line. Orthosiphol A had vasodilator effect and inhibited inflammation caused by TPA. Antimicrobial effect was showed by rosmarinic acid. No toxic effects were found after acute and subchronic administration. Clinical study showed that after 12 weeks treatment, systolic and diastolic blood pressures were decreased. No changes were found in plasma electrolytes, lipid, and blood glucose levels. We conclude that traditionally use of *O. stamineus* meets its scientific evidence in aspects of phytochemical, pharmacological, toxicological as well as clinical.

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