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OVERVIEW OF EFFICACY, SAFETY AND PHYTOCHEMICAL STUDY OF ANREDERA CORDIFOLIA (TEN.) STEENIS

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Abstract

Anredera cordifolia (Ten.) Steenis is used for medical purposes. In this article, traditional usage, phytochemical content, pharmacology activity and toxicity test result of *A. cordifolia* will be summarized. Terpenoids, steroid, glycoside, flavonoids, saponins and alkaloids were found in *A. cordifolia*. Apart from that, some pure compounds such as ursolic acid, ancordin, apigenin, etc. were isolated from this plant. *A. cordifolia* was proven to have benefits in repairing kidney function, as antibacterial, antifungal, antivirus, protease inhibitor, xanthine oxidase inhibitor, antidiabetic, antihypertensive, vasodilator, diuretic, anti-obesity, hypolipidemic, antioxidant, gastroprotective, hepatoprotective, cytotoxic, anti-inflammatory, analgesic and wound healing. Toxicity test result showed that ethanol extract of *A. cordifolia* leaves can be safely consumed. Scientific result showed that *A. cordifolia* is potential to be developed as medicinal plant.

Keywords: *Anredera cordifolia*, phytochemical content, pharmacology, toxicology

Introduction

Anredera cordifolia (Ten.) Steenis is grouped as vines with tender and cylindrical intertwined stem. It has green heart-shaped leaves and tuber on its roots or axillary [1]. This basellaceae family-origin plant has synonim names ie *Boussingautia cordifolia* Ten., *B. gracilis* Miers, *A. cordifolia* subsp. Gracilis (Miers), *B. gracilis* f. pseudobaselloides Hauman, *B. gracilis* var pseudobaselloides (Hauman) Bailey, *B. gracilis* f. typica (Hauman) and *B. cordata* Sprenger [2,3]. *A. cordifolia* is also known as Madeira vine, potato vine, lamb's tail vine, mignonette vine, heart-leaf Madeira vine, jalap vine, white shroud, enredadera del mosquito, enredera papa [1], malabar spinach (India) [4], speck blatter/fat leaf/bacon leaf (Jerman) [5], and binahong (Indonesia) [6]. *A.cordifolia* is South American native plants, distributed from Paraguay up to southern Brazil and northern Argentina. Currently, it has been globally distributed through China, Japan, Israel, India, some part of Africa, USA, Mexico, Caribbean, Australia, New Zealand and its surrounding islands and it showed that this plant can grow in subtropical and tropical climate areas [7]. In Australia and African forests, these plants are prohibited because they are invasive and can harm origin plant from those countries [1,7]. Meanwhile in other countries, this plant is used as traditional medicine. Brazilian people used *A. cordifolia* leaves to traditionally cure wounds from animal bite (dog and spider) or infected wounds [5]. In Zenta River basin (northwest Argentina), *A. cordifolia* stem is used to cure headache and toothache [8]. Until now, the data of efficacy of *A. cordifolia* is still limited, there are only several scientific researches published *A. cordifolia* which proved that this plant is potential to be developed as medicinal plant. So that, it is important to gather researches related to phytochemical content, pharmacology activity and toxicity test result of *A. cordifolia*.

Methods

Data in this article are collected from literature study throughout local or international scientific journals in Scopus portal and Google scholar.

Results and Discussion

Phytochemical content of Anredera cordifolia (Ten) Steenis

Phytochemical screening result from stem, leaves and tuber of *A. cordifolia* showed terpenoids, steroid, glycoside and alkaloid contents. Meanwhile, its flower contained terpenoids, steroid and glycoside [9]. Lin et al. research showed that *A. cordifolia* contained triterpenoid sapogenins which were ethyl 3β-hydroxy-30-horoleana-12, 18-dien-29-oate, larreaganin A, 3β-hydroxy-30-horoleana-12,19-dien-28-oic oate with its ethyl ester and 28-ethyl hydrogen-3β-hydroxyolean-12-ene-28,29-dioate [10]. Abou-Zeid et al. identified the essential oil main component of *A. cordifolia* herbs, which were phytol, α-pinen, and 6,10,14- trimethyl pentadecanone [11]. *A. cordifolia* tuber contained triterpenoid saponin boussingoside E and quinosaponin-9 [12].

Three flavonoid isolates were obtained from butanol fraction of ethanol extract of *A. cordifolia* leaves. There were identified as flavone that has 7-OH and predicted having one sugar (monoglycoside) attached to O- on C-5, flavone which has –OH on C-7 and predicted having 5-OH without -OH on C-4, flavone that has 7-OH and *o*-diOH on B ring and predicted having sugar attached to C-5[13]. Flavonoid from ethyl acetate extract of *A. cordifolia* leaves was identified as 3, 5, 3',4'- tetrahydroxyflavonol [14]. Methanol extract of *A. cordifolia* leaves contained 8-glucopyranosyl-4',5,7-trihydroxyflavone compound [15], and boussingoside (A_1, A_2, B, and C), momordin, and larreagenin A [16]. Alkaloid (bethanidine) and phenolic acid (p-coumaric acid) compounds were expected to be found in ethanol extract of *A. cordifolia* leaves [17,18]. Ursolic acid was also found in *A. cordifolia* leaves [19]. Qiong et al. research found two flavanols and four flavones in *A. cordifolia* which were bougracol A, 4,7-dihydroxy- 5-methoxy – 8– methyl –6 - formyl- flavane, 7-O-methylunonal, 5,7-dihydroxy-6,8-dimethyl-2-phenyl-4H-1-benzopyran-4-one, desmosflavone and demethoxymatteucinol [20].

Pharmacology Activities of Anredera cordifolia (Ten.) Steenis

Some scientific research had proven that *A. cordifolia* had pharmacological activity in repairing kidney function, as antibacterial, antifungal, antivirus, protease inhibitor, xanthine oxidase inhibitor, antidiabetic, antihypertensive, vasodilator, diuretic, anti-obesity, hypolipidemic, antioxidant, gastroprotective, hepatoprotective, cytotoxic, anti-inflammatory, analgesic and wound healing

Kidney Function Repair

Ethanol extract of *A. cordifolia* leaves at 50, 100, and 150 mg/kg bw that were administered for 4 weeks could reduce significantly creatinine serum and urea level in rats induced by gentamycin and piroxicam. *A. cordifolia* extract at dose of 150 mg/kg bw. significantly influenced renal index (kidneys weight/rat's body weight). The test group 150 mg/kg bw had significant difference renal index

compared to positive control group ($p<0.05$) and no significant difference compared to normal control group. This result was supported with histopathological observation of kidney which showed at 150 mg/kg bw, didn't revealed the presence of glomerular cell segmentation on rats. This study suggested that leaves extract of *A. cordifolia* at dose of 150 mg/kg bw may be able to prevent or even repair damage that occurred to cells [21].

A research had been conducted to *A. cordifolia* leaves and corn silk extracts towards rat model kidney failure. Administration of extract with single-dose; half single-dose extract combination (50 mg/kg bw of *A. cordifolia* and 37,5 mg/kg bw of corn silk); single-dose extract combination (100 mg/kg bw of *A. cordifolia* and 75 mg/kg bw of corn silk) could reduce level of creatinine, urea and TBARS (*Thiobarbituric Acid Reactive* Substances), enhancement of catalase enzyme level and SOD (Superoxide Dismutase), and also renal histopathologic repair especially in medulla part. This research also showed that administration of half single-dose extract combination gave additive effect and better than single-dose and single-dose extract combination administration [22].

Antibacterial and Antifungal

Antibacterial activity study of ethanol extract from *A. cordifolia* leaves expressed that the extract could inhibit the growth of *Bacillus cereus* KTCC 1061, *B. subtilis* KTCC 1021, *Escherichia coli* H7 (O156), *Pseudomonas aeruginosa*, Methicillin-Resistant Coagulase-Negative Staphylococcus (MRCNS), Methicillin-Sensitive *Staphylococcus aureus* (MSSA), Methicillin-Susceptible Coagulase-Negative Staphylococcus (MSCNS), Methicillin-Resistant *Staphylococcus aureus* (MRSA), and Vancomycin-Resistant Enterococcus (VRE) with MIC (µg/mL) 256, 256, 256, 256, 512, 512, 1024, >2048 and 1024, respectively [23]. Triterpenoid in the hexane extract of *A. cordifolia* leaves inhibited *E. coli* and *Staphylococcus aureus* growth with zone of inhibition of ≤ 5 mm [24]. The hexane, ethyl acetate and 70% ethanol extracts of *A. cordifolia* leaves inhibited *S. aureus* growth with MIC 17 mg/mL, 7 mg/mL, and 5 mg/mL, respectively [25]. The ethanol extract of *A. cordifolia* leaves had activity againts bacteria growth in recurrent aphthous stomatitis with MIC 6.25% [26]. Beside that, the ethanolic extract could inhibit *Streptococcus mutans* with zone of inhibiton of 8.3 mm [27]. The water extract of *A. cordifolia* leaves revealed inhibition towards *B. subtilis* ATCC 6633, *E. coli* ATCC 11105, *S. aureus* ATCC 6538, and *P. aeruginosa* ATCC 15153 growth [28]. A test with 100% concentration of water extract from *A. cordifolia* leaves essence (1 g/mL) showed inhibition towards *B. cereus* and *Salmonella enteritidis* 9.64 and 6.86 mm, respectively [29]. *A. cordifolia* leaves juice could inhibit *E. coli* ATCC 25922 growth, which its inhibitory zone diameter increase along with increasing in juice concentration [30].

A. cordifolia seed was an ingredient in herbal remedy used in gonorrhea treatment in South Africa. This herbal remedy revealed moderate activity against *Neisseria gonorrhoeae* ATCC 49226 (66%), but was proven to have good activity against *S. aureus* ATCC 12600, *E. coli* ATCC 11775, and *K. pneumonia* ATCC 13883 growth with MIC 0.78 mg/mL, 1.56 mg/mL, and 0.78 mg/mL, respectively [31]. The water extract of *A. cordifolia* roots inhibit *Bacillus pumilus* and *Enterobacter cloacae* growth with MIC 50 mg/mL. The chloroform extract of *A. cordifolia* root inhibit *B. pumilus* and *E. cloacae* with MIC 60 and 50 mg/mL respectively. The water and chloroform extracts of *A. cordifolia* root inhibit *B. subtilis*, *S. aureus*, *E. coli*, *K. pneumonia*, *P. aeruginosa*, *Serratia marcescens*, and *E. aerogenes* with MIC 60 mg/mL [32]. Etanolic extract (70%) of *A. cordifolia* stem at 86% (b/v) concentration could stop of *Candida albicans* growth [33].

Antivirus

Flavonoids from *A. cordifolia* that were found by Qiong et al., bougracol A, *4,7-dihydroxy-5-methoxy-8-methyl-6-formyl-flavane*, and *demethoxymatteucinol* presented weak anti-HIV activity with EC_{50} 45.09, 48.73, 55.47, and 82.75 µmol/L, respectively, and had TI (Trypsin Inhibitor) value 1.41, 1.20, 7.15 and >8.51, respectively [20].

Protease Inhibitor

Ancordin, the major rhizome protein from *A. cordifolia* stimulated nitrite oxide production in RAW264.7 cell without showing any cytotoxic effect. The stimulation itself depended on dose that was given. Besides, based on the obtained calculation, purified protein revealed 0.0428 µg trypsin inhibition for every µg of ancordin [34].

Xanthine Oxidase Inhibitory Activity

The ethanol extract of *A. cordifolia* herbs could inhibit xanthine oxidase with IC_{50} 66.20 µg/mL. In this study, allopurinol was used as reference drug with IC_{50} 4.84 µg/mL [35]. Previous study was also conducted in ethanol extract of *A. cordifolia* leaves and its combination with *Sonchus arvensis* leaves with ratio 1:1. Both of samples gave IC_{50} 635.25 and 846.32 µg/mL, respectively [36]. Both research results showed that herbs gave better xanthine oxidase inhibitory activity than leaves.

Antidiabetic

Antidiabetic activity in *A. cordifolia* was performed through *in vitro* and *in vivo* tests. *In vitro* test was conducted towards α-glucosidase, α-amylase and

dipeptidyl peptidase IV (DPP IV) enzymes. α-glucosidase and α-amylase inhibition would reduce hyperglycemic condition after meal by delaying glucose absorption process because both enzymes had role in carbohydrate hydrolysis process. DPP IV had role in incretin degradation process, especially GLP-1 (Glucagon Like Peptide-1) that stimulated insulin production [37]. Elya et al. research result reported that the ethanol extract of *A. cordifolia* leaves could inhibit α-glucosidase with IC_{50} 54.24 µg/mL, while extract 62.5 µg/mL also gave 74.03% inhibition to α-amylase and 10.70% inhibition to DPP IV [38]. Methanol extract of *A. cordifolia* leaves at dose of 50 and 200 mg/kg bw significantly reduce blood glucose level in alloxan induced-rats by 61.02% and 60.68% on the 7^{th} day; 75.64% and 66.61% on the 14^{th} day. Histopathology results revealed reducing in damage of β-pancreas cells [39]. The water extract which was obtained from *A. cordifolia* aerial part (equal to 10 g dry aerial part/kg bw) could reduce rats glucose level from >399 mg/% to 60 mg/%. The similar result was obtained by 20 mg/kg bw of Boussingoside A1 that was successfully isolated. While Boussingoside A2, B and C gave weaker hypoglycemic activities than Boussingoside A1[16].

Antihypertensive

Antihypertensive effect was observed in rats that were induced by adrenaline. Ethanol extract of *A. cordifolia* leaves at doses of 50, 100, 150 mg/kg bw could prevent significantly increase in heart rate compared to negative control group ($p<0.05$). Only ethanol extract 50 mg/kg bw revealed diuretic effect although it was weaker than furosemide. Antihypertensive effect from *A. cordifolia* was expected to happen through β-adrenergic receptor inhibition and natriuretic effect [40].

Vasodilator

The ethanol (70%) extract of *A. cordifolia* leaves (0.9 mg/mL) showed significant vasodilation effect in norepinephrine pre-contracted rabbit aortic rings, but no vasodilation effect in the KCl pre-contracted rabbit aortic rings. Mechanism of ethanol extract from *A. cordifolia* leaves was expected from nitrite oxide [41].

Anti-obesity

A. cordifolia ethanol extract at doses of 300, 600, and 900 mg/kg bw could reduce body weight gain, serum and hepatic lipid levels in high-fat diet induced obese rat. There was an increase in gene expression for PPAR (Peroxisome Proliferator-Activated Receptor) α, fatty acid oxidation, thermogenesis-related proteins-acyl-coenzyme A oxidase, carnitine palmitoyl transferase-1, and uncoupling protein-2 in liver. Moreover, the extract could also suppress sterol regulatory element binding protein-1, lipogenic gene, fatty acid synthase and PPARγ in adipose tissues and liver. This result demonstrated that anti-obesity and hipolipidemic effect from ethanol extract were expected from gene expression regulation that was involved in lipolysis and lipogenesis [42]. Molecular mechanism from this extract was then investigated further by Kim and Choung. The ethanol extract of *A. cordifolia* at dose of 100 µg/mL could decrease 31% of free fatty acid, it suggest that extract can reduce lipid accumulation in 3T3-L1 cells undergoing differention to adipocytes. Extract increased phosphorylation of AMP-activated kinase (AMPK), which is one of the rate-limiting enzyme in fatty acid synthesis pathway. Based on this result, ethanol extract of *A. cordifolia* leaves was expected to give anti-adipogenic effects through AMPK activity regulation and gene expression that was involved in lipogenesis [43]. Another test conducted by Sukandar et al. denoted that 96% ethanol extract of *A. cordifolia* leaves at dose of 100 mg/kg bw gave the lowest body weight increase compared to others group and had better activity than positive control group and orlistat 21.6 mg/kg bw in high-carbohydrate diet induced-rats. This anti-obesity effect was not followed by appetite lost [44].

Anti-dyslipidemia

Ethanol extract from *A. cordifolia* leaves at doses of 50, 100, 200 mg/kg bw could significantly reduce 55.25%, 63.45%, and 67.70% cholesterol level; 81.31%, 89.01% and 95.33% LDL level; 41.08%, 47.59%, and 50.66% triglyceride level respectively; but extracts at these doses didn't give effect to HDL level. Moreover, extract administration also caused fat deposit decrease inside endothelial cells in blood vessels [45]. Anti-hypercholesterolemia *in vitro* test with malondialdehyde (MDA) enzyme and 8-hydroxy-diguanosine (end product from lipid peroxidation process) showed that ethanol extract 100 mg/kg bw could reduce MDA and 8-hydroxy-diguanosine level [46].

Antioxidant

Antioxidant *in vitro* test was conducted with few methods, such as DPPH free radical, TEAC and ORAC assay. Methanol extract of *A. cordifolia* leaves could scavenge DPPH radical with IC_{50} 53.11 µg/mL. Fractionation from ethanol extract were hexane, ethyl acetate, and butanol fractions gave IC_{50} DPPH 256.23, 57.96, and 132.39 µg/mL, respectively. The 8-glucopyranosyl-4',5,7-trihydroxyflavone compound that was successfully isolated from ethyl acetate extract of *A. cordifolia* leaves could scavenge DPPH radical with IC_{50} 68.07 µg/mL [15]. *A. cordifolia* extract with 18 mg/g total polyphenol (equal to chlorogenic acid) could inhibit DPPH radical with IC_{50} 1572.9 µg/mL [47]. Chao et al. tested the

antioxidant activity of *A. cordifolia* leaves extract with various methods. The result exposed that methanolic extract had IC_{50} of DPPH 1173.32 µg/mL. By using TEAC assay, methanolic extract gave IC_{50} 36.22 µg/mL while ethanolic extract 21.04 µg/mL. Its means ethanolic extract gave higher antioxidant activity than methanolic extract, by TEAC assay. Meanwhile by using ORAC assay, extract exhibited antioxidant activity with ORAC-hydrophilic value 202. 59 µmol Trolox/g dry weight and ORAC-lipophilic value 157.75 µmol Trolox/g dry weight. It was indicated that hydrophilic extract was more effective than lipophilic extract. Phytochemical screening result showed that *A. cordifolia* extract contained polyphenol (equal to 5.81 mg gallic acid/g dry weight), flavonoid (equal to 40 mg quercetin/g dry weight), flavonol (equal to 6.92 mg quercetin/g dry weight, 781. 28 µg myricetin/g dry weight, 455.16 µg morin/g dry weight) [48].

Gastroprotective

A. cordifolia extract at doses of 250, 500, 1250 mg mg/kg bw significantly reduce ulcer index (16.0%, 12.6%, 16.2 %, respectively) compared to negative control (31.1%). Moreover, extract administration also reduced lesion in gastric mucosa in ethanol-induced rats [49].

Hepatoprotective

The water extract from *A. cordifolia* leaves, stem and bud decreased SGOT and SGPT level in rat with liver damage that was induced by either CCl_4 or D-GalN. Histopathological change in liver such as necrosis, fat accumulation, ballooning degeneration, inflammatory infiltration of lymphocyte and Kupffer cell around central vein for CCl_4-induced hepatotoxicity and portal vein for D-GalN-induced hepatotoxicity, were simultaneously improved with the three extracts administration [50].

Analgesic

Ethanol extract of *A. cordifolia* leaves at doses of 100, 200, and 400 mg/kg bw were proven to give analgesic effect. Plantar test showed that in the animal test observation at 1 hour after they were given by 3 doses, time to feel early pain was longer than negative control group, whereas dose increase was directly proportional with duration of early pain. At dose of 400 mg/kg bw, analgesic effect of the extract was comparable with positive control group, diclofenac sodium (2.25 mg/kg bw). Through this test, analgesic effect of extract was expected by inhibiting prostaglandin synthesis [51].

Cytotoxic

Cytotoxic test from ethanol extract of *A. cordifolia* leaves performed with MTT assay using HeLa cell and apoptosis-induced test with annexin V-FITC. Extract denoted cytotoxic effect and it started apoptosis in HeLa cell at IC_{50} 75 µg/mL. Extract administration didn't show increase of p53 expression level in cell. The result of this research revealed that cytotoxic activity of *A. cordifolia* leaves towards HeLa cell was through p53 pathway [52].

Wound Healingh

Test result from *A. cordifolia* leaves extract ointment at 10, 20, and 40% concentration in rabbit with *S. aureus* infection wound showed better recovery effect along with increasing in extract concentration. Recovery effect was observed from infection wound length that keeps shrinking [53]. Research which was conducted by Istyastono and Yuliani found that *A. cordifolia* leaves extract addition into celecoxib gel could accelerate wound healing process (showed by decreasing in wound scar) compared to celecoxib gel only [54]. *A. cordifolia* leaves which was used in patient with partial thickness burn wound also showed recovery in epithelialization with no further infection [55].

Toxicity Study

Acute toxicity test result of ethanol extract of *A. cordifolia* leaves showed no mortality in ddY mice until highest dose of 15 g/kg bw. In sub-chronic toxicity test, extract up to dose 1 g/kg bw didn't cause mortality and behavioral change. There was no significant difference in body weight, organ weight, hematology, and blood biochemistry test. Histology observation showed no difference in heart, lungs, liver, and kidney compared to normal control group. These results showed that ethanol extract of *A. cordifolia* leaves didn't give toxic and abnormality symptoms, so it could be considered as safe for medical purpose [56]. Teratogenicity test showed that ethanol extract of *A. cordifolia* leaves at doses of 100, 400, and 1000 mg/kg bw didn't have teratogenic effect [57].

Anredera cordifolia has potentials as medicinal plant. Based on the general explored research results, *A. cordifolia* could be used to cure degenerative diseases such as hypertension, diabetes, dyslipidemia, obesity and can act as gastroprotective and hepatoprotective. Free radical is also a trigger to degenerative diseases. Proof of the antioxidant activity from *A. cordifolia* can be used as a start data to develop degenerative diseases research. Due to limited active compound research of *A. cordifolia*, there are still chances for world-wide researchers to explore the use of this plant.

References

1. Vivian-Smith G, Lawson BE, Turnbull I, et al. The biology Australian weeds. 46. *Anredera cordifolia* (Ten.) Steenis. Plant Prot Q 2007; 22 (1).
2. Eriksson R. A synopsis of Basellaceae. Kew Bulletin 2007; 62 (2): 297-320.
3. Wagner WL, Herbst DR, Sohmer SH. Manual of flowering plants of Hawaii. Vol. 2. Honolulu, HI, USA: Bishop Museum Special Publication 83, 2011: 381.
4. Prasuna CPL, Chakradhar RPS, Rao JL, et al. EPR and IR spectral investigations on some leafy vegetables of Indian Origin. Spectrochim Acta A 2008; 74: 140-47.
5. Heisler EV, Badke MR, Andrade A, et al. Popular knowledge about the use of plant *Anredera cordifolia* (Fat Leaf). Text & Context Nursing Journal 2012; 21(4): 937-44.
6. BPOM. Collection of Medicinal Plants Taxonomy in Medicinal Plant Garden at Citeureup. Indonesia National Agency of Drug and Food Control. Jakarta.
7. Cagnotti C, McKay F, Gandolfo D. Biology and host specificity of *Plectonycha correntina* Lacordaire (Chrysomelidae), a candidate for the biological control of *Anredera cordifolia* (Tenore) Steenis (Basellaceae). Afr Entomol 2007; 15(2):300-309.
8. Hilgert NI. Plants used in home medicine in the Zenta River basin, Northwest Argentina. J Ethnopharmacol 2001; 76(1):11-34.
9. Sakinah MAM, Astuti SM, Andayani RBM, et al. Determination of saponin compound from *Anredera cordifolia* (Ten) Steenis plant (Binahong) to potential treatment for several diseases. JAS 2011; 3(4), 224-232.
10. Lin H-Y, Kuo S-C, Chao P-DL, et al. A new sapogenin from *Boussingaultia gracilis*. J Nat Prod 1988; 51(4), 797-798.
11. Abou-Zeid AHS, Soliman FM, Sleem AA, et al. Phytochemical and bio-activity investigations of the aerial parts of *Anredera cordifolia* (Ten.) Steenis. Bull Nat Res Cent Egypt 2007; 32 (1): 1-33.
12. Espada A, Riguera R. Boussingoside E. a new triterpenoid saponin from the tubers of *Boussingautia basseloides*. J Nat Prod 1997; 60:17-19.
13. Lestari AS. Isolation and characterization of flavonoids from ethanol extract of binahong leaves (*Anredera cordifolia* (Ten.) Steenis). Bandung Institute of Technology: Thesis, 2013: 22, 24, 26.
14. Rahmawati L, Fachriyah E, Kusrini D. Isolation, identification, and antioxidant activity test of flavonoids compound from binahong leaves. Chem Info 2013; 1(1): 165-173.
15. Djamil R, Wahyudi PS, Wahono S, et al. Antioxidant activity of flavonoid from *Anredera cordifolia* (Ten.) Steenis Leaves. Int Res J Pharm 2012; **3** (9): 241 - 243.
16. Espada A, Rodiruguez J, Villaverde MC, et al. Hypoglucaemic triterpenoid saponin from *Boussingaultia baselloides*. Can J Chem 1990; 68(11): 2039-44.
17. Ekaviantiwi TA, Fachriyah E, Kusrini D. Identification of phenolic acid from ethanolic extract of Binahong (*Anredera cordifolia* (Ten.) Steenis) leaves and its antioxidant activity. Chem Info 2013; 1(1): 283-93.
18. Marwoko MTB, Fachriyah E, Kusrini D. Isolation, identification, and antioxidant activity test of alkaloid compound from Binahong (*Anredera cordifolia* (Ten.) Steenis) leaves. Chem Info 2013; 1(1): 196-201.
19. Yuliani SH, Istyastono E.P. Factorial design application to study ursolic acid extraction process from Binahong (*Anredera cordifolia* (Ten) Steenis). Medicinus 2013; 26(1): 35-39.
20. Qiong GU, MA Yun-Bao MA, Xue-Mei Z, et al. One new flavanoid and anti-HIV active constituents from *Boussingaultia gracilis* Miers var. pseudobaselloides Bailey [J]. *Chem* J Chinese U 2007; 28(8): 1508-1511.
21. Sukandar EY, Fidrianny I, Adiwibowo LF. Efficacy of ethanol extract of *Anredera cordifolia* (Ten.) Steenis leaves on improving kidney failure in rats. Int J Pharmacol 2011; **7**(8): 850-855.
22. Sukandar EY, Sigit JI, Adiwibowo LF. Study of kidney repair mechanism of Corn Silk (*Zea mays* L. Hair)-Binahong (*Anredera cordifolia* (Ten.) Steenis) leaves combination in Rat Model of kidney failure. Int J Pharmacol 2013; 9(1): 12-23.
23. Garmana AN, Sukandar EY, Fidrianny I. Activity of several plant extracts against drug-sensitive and drug-resistent microbes. Procedia Chem 2012; 13: 164 - 169.
24. Murdianto AR. Isolation, identification and testing antibacterial activity of triterpenoid compound from Binahong (*Anredera cordiofolia* (Ten.) Steenis) leaves extract against *Staphylococcus aureus* and *Escherichia coli*. Chem Info 2013; 1(1): 328 - 336.
25. Iras. Antibacterial activity of n-hexane, ethyl acetate, and ethanolic 70% extract of Binahong (*Anredera cordiofolia* (Ten.) Steen) leaves towards *Staphylococcus aureus* growth. University of Jember: Thesis, 2008.
26. Ying LY, Hernawan I, Hendarti HT. Inhibition effect of binahong (*Anredera cordifolia* (Ten.) Steenis) leaf extract towards polybacteria of recurrent aphthous stomatitis. Oral Med Dent J 2011; 3(2): 18-26.

27. Rimporok S, Kepel BJ, Siagian KV. Study of effectivity of binahong (*Anredera cordifolia* Steenis) leaves extract towards *Streptococcus mutans* growth. Pharmacon 2015; 4(4): 15-21
28. Paz EA, Cerdeiras M.P, Fernandez J, et al. Screening of Uruguayan medicinal plants for antimicrobial activity. .J Ethnopharmacol 1995; 45: 67-70.
29. Rahmawati F, Bintari SH. Antibacterial activity of the binahong (*Anredera cordifolia*) leaf extract towards *Bacillus cereus* and *Salmonella enteritidis* growth. Unnes J Life Sci 2014; 3(2): 103-111.
30. Darsana IGO, Besung INK, Mahatmi H. Potential of binahong (*Anredera cordifolia* (Tenore) Steenis) leaves in inhibiting growth of *Escherichia coli*, *in vitro* study. Ind Med Vet 2012; 1(3) 337-351.
31. Mulaudzi RB, Ndhlala AR, Van Staden J. Ethnopharmacological evaluation of a traditional herbal remedy used to treat gonorrhea in Limpopo province, South Africa. S Afr J Bot 2015; 97: 117-122.
32. Tsikalange TE, Meyer JJM, Hussein AA. Antimicrobial activity, toxicity, and the isolation of a bioactive compound from plants used to treat sexually transmitted diseases. J Ethnopharmacol 2005; 96: 515-519
33. Kumalasari E, Sulistyani N. Antifungal activity of ethanol extract of Binahong (*Anredera cordifolia* (Tenore) Steen.) stem against *Candida albicans* and its phytochemical screening. J Ilmiah Kefarmasian 2011; 1(2): 51-62.
34. Chuang M-T, Lin Y-S, Hou WC. Ancordin, the major rhizome protein of madeira-vine, with trypsin inhibitory and stimulatory activities in nitric oxide productions. Peptides 2007; 28(6): 1311-1316.
35. Hendriani R, Sukandar EY, Anggadiredja K, et al. *In vitro* evaluation of xanthine oxidase inhibitory activity of selected medicinal plants. Int J Pharm Clin Res 2016; 8(4): 235-8.
36. Widyarini KD, Sukandar EY, Fidrianny I. Xanthine oxidase inhibitory and antihyperuricemic of *Anredera cordifolia* (Ten.) Steenis, *Sonchus arvensis* L., and its combination. Int J Pharm Pharm Sci 2015; 7(3): 86-90.
37. Ban K, Hui S, Drucker DJ, et al. Cardiovascular consequences of drugs used for the treatment of diabetes: Potential promise of incretin-based therapies. J Am Soc Hyperten 2009; 3: 245-259.
38. Elya B, Handayani R, Sauriasari R, et al. Antidiabetic activity and phytochemical screening of extracts from Indonesian plants by inhibition of alpha amylase, alpha glucosidase and dipeptidyl peptidase IV. Pak J Biol Sci 2015; 18(6): 279-284.
39. Sukandar EY, Qowwiyah A, Larasari L. Effect of methanol extract heartleaf Madeira vine (*Anredera cordifolia* (Tenore) Steenis) leaves on blood sugar in diabetes mellitus model mice. J Medika Planta 2011; 1(4): 1-10.
40. Garmana AN, Sukandar EY, Fidrianny I. Preliminary study of blood pressure lowering effect of *Anredera cordifolia* (Ten.) Steenis on wistar rat. Int J Pharmacogn Phytochem Res 2016; 8(2): 300-304.
41. Sukandar EY, Ridwan A, Sukmawan YP. Vasodilation effect of ethanolic extract of *Anredera cordifolia*, *Sonchus arvensis* L, and ursolic acid on isolated rabbit aortic and frog heart. Int J Pharm Pharm Sci 2016; 8(2): 145-149.
42. Wang L, Bang C-Y, Choung S-Y. Anti-obesity and hypolipidemic effects of *Boussingaultia gracilis* Miers var pseudobaselloides Bailey in obese rats. J Med Food 2011; 14: 17-25
43. Kim H, Choung S-Y. Anti-obesity effect of *Boussingaultia gracilis* Miers var. pseudobaselloides Bailey via activation of AMP-activated protein kinase in 3T3-L1 cells. J Med Food 2012; 15(9): 811-817.
44. Sukandar EY, Kurniati NF, Nurdianti AN. Antiobesity effect of ethanol extract of *Anredera cordifolia* (Ten.) Steenis leaves on obese male Wistar rats induced by high-carbohydrate diet. Int J Pharm Pharm Sci 2016; 8(4): 171-173.
45. Lestari D, Sukandar EY, Fidrianny I. *Anredera cordifolia* leaves extract as antihiperlipidemia and endothelial fat content reducer in male Wistar rat. Int J Pharm Pharm Sci 2015; 7(6): 435-439.
46. Wahjuni S. Anti-hipercholesterolemia of *Anredera cordifolia* in hypercholesterolemia rat wistar through decrease of malondialdehyde and 8-hydroxy-diguanosine. Int J Biomed Sci 2014; 8(1): 4-7.
47. Shieh P-C, Agoramoorthy G, Kuo D-H. Evaluation of antioxidant polyphenols in Taiwan's medicinal plants. Asian J Chem 2009; 21(7): 5556-5562.
48. Chao P-Y, Lin S-Y, Lin K-H, et al. Antioxidant activity in extracts of 27 Indigenous Taiwanese vegetables. Nutrients 2014; 6: 2115-2130.
49. Horng C-T, Chao H-R, Lee C-F, et al. Gastro protective effect of madeira vine against ethanol-induced gastric mucosal lesion in rat. Asian J Chem 2012; 24 (2): 765-768.
50. Li CC, Sung TC, Yen MH. The anti-inflammatory and liver protective effect of *Bousingaultia gracilis* var pseudobaselloides extract in rats. Phytother Res 1994; 8(4): 201-207.

51. Yuliani SH, Anggraeni CD, Sekarjati W, et al. Cytotoxic activity of *Anredera cordifolia* leaf extract on hela cervical cancer cells through p53-independent pathway. *Asian* J Pharm Clin Res 2015; 8(2): 328 – 331.
52. Yuziani, Harahap U, Karsono. Evaluation of analgesic activities of ethanolic extract of *Anredera cordifolia* (Ten.) Steenis leaf. *Int J* PharmTech Res 2014; 6(5): 1608-1610.
53. Paju N, Yamlean PVY, Kojong N. Study the effectivity of Binahong (*Anredera cordifolia*(Ten.) Steenis) leaf extract ointment on rabbit (*Oryctolagus cuniculus*) that infected by *Staphylococcus aureus*. Pharmacon 2013; 2(1): 51-61.
54. Istyastono EP, Yuliani SH. Scarless wound healing gel with Binahong (*Anredera cordifolia* (Ten.) Steenis) leaves extract and celecoxib as the active ingredients. AIP Conf Proc 2016; 1755 (160001): 1-5.
55. Prasetyo AT, Herihadi E. The application of moist exposed burn ointment (MEBO) and Binahong leaves in Treating partial thickness burn. Jurnal Plastik Rekonstruksi 2013; 3: 142-146.
56. Salasanti CD, Sukandar EY, Fidrianny I. Acute and sub chronic toxicity study of ethanol extract of Anredera *cordifolia* (Ten) Steenis leaves. Int J Pharm Pharm Sci 2014; 6(5): 348-352.
57. Sukandar EY, Kurniati NF, Fitri V. Evaluation of teratogenicity effects of ethanol extract of Binahong leaves (*Anredera cordifolia* (Ten) Steenis) in Wistar rat. Int J Pharm Pharm Sci 2014; 6(11): 422-426.