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 synonym 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, enredadera papa [1], malabar spinach (India) [4], speck blatter/fat leaf/bacon leaf (German) [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. researched that A. cordifolia contained triterpenoid sapogenins which were ethyl 3β-hydroxy-30-horleana-12, 18-dien-29-oate, larreaganin A, 3β-hydroxy-30-horleana-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-pinene, and 6,10,14-trimethyl pentadecanone [11]. A. cordifolia tuber contained triterpenoid saponin boussingoside E and quinonosaponin-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 (Aα, Aβ, B, and C), momordin, and larreagenin A [16]. Alkaloid (benthidine) 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, antiabietic, 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 (MRCSN), 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 against bacteria growth in recurrent apthous 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 6.64 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]. Ethanolic 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 EC₅₀ 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 IC₅₀ 66.20 μg/mL. In this study, allopurinol was used as reference drug with IC₅₀ 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 IC₅₀ 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\textsubscript{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 7th day; 75.64% and 66.61% on the 14th 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 hypoglycemiac 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 vasodilatation effect in norepinephrine pre-contracted rabbit aortic rings, but no vasodilatation 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 differentiation 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\textsubscript{50} 53.11 μg/mL. Fractionation from ethanol extract were hexane, ethyl acetate, and butanol fractions gave IC\textsubscript{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\textsubscript{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\textsubscript{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 IC₅₀ of DPPH 1173.32 μg/mL. By using TEAC assay, methanolic extract gave IC₅₀ 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), flavanol (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/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 CCl₄ 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 CCl₄-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 IC₅₀ 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 Iyastono 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.
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