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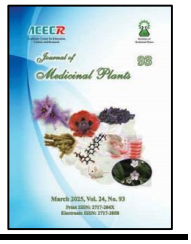

Research Article

Antioxidant and acetylcholinesterase inhibitory activities of Indonesian cultivated medicinal plants

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ABSTRACT

Background: Throughout many decades, researchers all around the world still extensively search for treatment strategies for Alzheimer's disease. Dispute the small number of medicines that can be used for the treatment, the side effects, and the only symptomatic treatments of the drug, which makes the necessity of finding new sources of drugs from plant sources a critical movement. **Objective:** In this research, we investigate the potential of 33 traditional medicines plants from Indonesia for their acetylcholinesterase inhibitor and antioxidant properties. **Methods:** The inhibitory potential of acetylcholinesterase was carried out using spectrophotometry using acetylcholine as a substrate and antioxidant activity was measured using the FRAP method. **Results:** The results indicate that among the 33 plants, only seven plants with an acetylcholinesterase inhibitor (AChEI). Those plants are *Chromolaena odorata*, *Mikania scandes*, *Piper cubeba*, *Peperomia pellucida*, *Persea americana*, *Lycium barbarum* and *Phyllanthus niruri*. All the plant samples showed remarkable antioxidant potency with the range of value 4.11 – 52.65 mg/mL. **Conclusions:** *Persea americana* (Lauraceae) had the greatest AChEI with a value of 4.11 mg/mL, meanwhile *Piper cubeba* (Piperaceae) has the highest potency in scavenging free radicals with an FRAP Value of 10.89 mg/mL. There was no correlation between AChEI and Antioxidant potency.

1. Introduction

Alzheimer's disease (AD) is a neurological disorder characterized by reduced numbers of enzymes, almost 90% in the brain, used to decompose acetylcholine, shown by the gradual decline in cognitive function and memory [1, 2]. This disease is caused by the appearance of neurofibrillary tangles and plaque neuritis [3, 4]. Currently, it is not clear what causes damage and death of neurons in AD patients. Still, several causes, such as free radicals, excessive stimulation of neurotransmitter receptors, and increased Ca2+, are reported to play a role in AD patients. Nowadays, about 44 million people

Abbreviations: AChEI, Acetylcholinesterase inhibitor; AD, Alzheimer's disease; AChE, Acetylcholinesterase; CO, *Chromolaena odorata*; EO, Essential Oils; IC_{50}, Inhibition Concentration; LB, *Lycium barbarum*; MS, *Mikania scandes*; PA, *Persea Americana*; PC, *Piper cubeba*; PN, *Phyllanthus niruri*; PP, *Peperomia pellucida*; TPC, Total Phenolic Content; TFC, Total Flavanoid Content

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suffer from AD, and the prevalence of this disease increases exponentially with age, reaching approximately 10% at age 65 and reaching nearly 50% at age 85 [3, 5, 6]. This disease is predicted to become one of the leading causes of death in the world, and it is estimated that 115.4 million people in 2050 will be affected by this disease [7, 8, 9]. Recent studies have designated that women endure AD more compared to men [3]. The previous research also makes a relation or link between AD and some other neurodegenerative diseases, such as dilated cardiomyopathy, stroke, Parkinson's disease, traumatic brain injury, and dementia caused by neuronal degradation [10, 11, 12].

Many researchers link AD to Acetylcholinesterase (AChE). AChE is an enzyme in the hydrolase group responsible for breaking down acetylcholine through carboxylic acid ester bonds. AChE also takes responsibility for cell apoptosis, catecholaminergic–cholinergic balance, inflammation, and oxidative stress [13, 14, 15]. Through the fact that AChE inhibitors such as protamine, memantine, and tracine fail to cure the disease, only improve cognitive and memory symptoms in AD, and cause side effects such as dizziness, vomiting, gastrointestinal disturbance, nausea, diarrhea, and hepatotoxicity [15-23], this trigger the urgency to obtain candidates for acetylcholine inhibitor drugs derived from plants. Interestingly, for the last decade, a study reported that searching for AChE inhibitors from plants recorded as much as 15% of all ACh research [24]. Huperazine A, physostigmeine, and galantamine are some of the AChE inhibitors derived from plants [25]. Physostigmeine is isolated from *Physostigma venenosum*, a plant belonging to the Leguminosae tribe. Galanthamine is a bioactive compound that is widely found in the Amarylidaceae family. Huperzine A, an alkaloid derived from *Huperzia serrate* (Lycopodiaceae) [3, 4, 16]. The AChE inhibitors from plant generality are alkaloid compounds such as isoquinoline, indole, quinolizidine, steroidal alkaloid, and piperine. Phenolic compounds, flavonoids, and some terpenoids were also potent AChE inhibitors (AChEI) [19, 25, 26].

In this research, a preliminary study will be conducted of several plants from families known to contain an abundance of alkaloids and polyphenols in order to obtain the candidate samples that can inhibit acetylcholine and have antioxidant activity. Several preliminary studies have shown a link between acetylcholinestrase inhibitory activity and antioxidant activity, where the presence of antioxidant compounds can protect nerves from oxidative stress so that they can slow the development of AD [16, 27].

2. Materials and methods

2.1. Sample Collection and Preparation

The selection of plant parts and the type of solvent are adjusted to the regulations for making traditional medicines in Indonesia. The plant parts collected are healthy and not mouldy. The leaves used are leaves that are neither old nor too young. The criteria for the fruit used are ripe fruit. The rhizome part is approximately three months old. The plants used were determined and stored for herbarium samples at the Widya Mandala Pharmaceutical Botany Laboratory, Surabaya. The extraction method was maceration with the solvent used is 96% ethanol or a mixture of ethanol-water (70:30). Samples were stored at -20°C until testing.

2.2. Evaluation of AChEI

The AChEI activity was tested according to the research method developed by Ali-Shtayeh *et al*. (2014). Each plant extract was prepared at a

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concentrations range of 100 - 0.78 mg/ml). *β*-naphthyl acetate (Sigma Aldrich, Germany), AChE solution (Sigma Aldrich, Germany), and fast blue b salt (Sigma Aldrich, Germany) were used as a reagent for this method. Galanthamine hydrobromide (Sigma Aldrich, Germany) served as a positive control. The linear regression between sample concentration and the % of inhibition will be used to get IC_{50} values [28, 29].

2.3. Antioxidant assay using FRAP Method

The antioxidant activity was carried out according to the method used by Wijaya et al. (2020). The plant extract concentration used was 1.56-100 mg/mL. Trolox, Quercetin, Rutin, and Vitamin C were used as a reference antioxidant compound. The FRAP value was used to express the antioxidant activity of the sample, representing a sample concentration with an absorbance value equivalent to 1 mM of $FeSO_4$. The IC_{50} was determined by plotting the sample concentration against the value of absorbance at 593 nm [30].

2.4. Total Phenolic Content

This assay was executed according to Wijaya et al. (2020) using Folin-Ciocalteu (Sigma, Germany) and sodium carbonate (Brataco, Indonesia). The absorbance of the prepared sample mixture was read at 765 nm. Gallic acid (Sigma, Germany) was used for the standard curve, and the total phenolic content expressed of mg Gallic acid equivalents/g of the sample [30].

2.5. Total Flavonoid Content

Total flavonoid contents (TFC) in the sample extract were analyzed with aluminum chloride reagent using the colorimetric method adapted from Nurcholis et al. (2021). The amount of flavonoid was calculated using a quercetin (Sigma, Germany) calibration curve and was expressed as mg QE/g sample [31].

2.6. Statistical Analysis

All results in this study are the average of three repetitions expressed in values ± standard deviation (SD). Correlations between antioxidant and AChEI activity were examined using Pearson's correlation coefficient (r).

3. Results

Neurodegenerative diseases such as Alzheimer's disease have become a big concern worldwide in the last decade. Acetylcholinesterase (AChE) inhibition is one therapy to reduce the symptoms of AD, as this inhibition increases cholinergic activity in the brain. In this study, 33 plants in Indonesia were examined for their ability as acetylcholinesterase inhibitors and their antioxidant activity. The plant parts used in research vary, depending on the experiences of traditional use for those plants. Maceration with ethanol or a mixture of ethanol-water (70:30) was used, depending on the solubility and stability of the active compounds. The list of plants and the extraction method are shown in Table 1.

Table 2 shows the plant extract activity for antioxidants and AChEI. In this research, the total amount of phenols and flavonoids was also carried out to determine the correlation between antioxidant activity with the total amount of phenols and antioxidant activity with the total amount of flavonoids (Table 2 & Figure 1). Several studies have correlated the existence of a linear relationship between antioxidant and anti-cholinesterase activity. Figure 2-3 illustrates the relationship between the two in this research. Correlation data analysis was carried out using only the seven plants that provided data on antioxidant and anti-cholinesterase activity.

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Table 1. The list of the plants, part of used, specimen numbers and the extraction method

No	Plants	Common Name	Part of used	Family	Specimen Number	Extraction Method
1	*Persea americana*	Avocado	Leaves	Lauraceae	WM-P-005	Maceration-Ethanol 96%
2	*Muntingia calabura*	Jamaica cherry	Leaves	Tiliaceae	WM-M-007	Maceration-Ethanol 96%
3	*Acalypha indica*	Indian acalypha	Aerial part	Euphorbiaceae	WM-A-125	Maceration-Ethanol 96%
4	*Anredera cordifolia*	Madeira vine	Leaves	Basellaceae	WM-A-126	Maceration-Ethanol 96%
5	*Mangifera indica*	Mango	Leaves	Anacardiaceae	WM-M-008	Maceration-Ethanol 96%
6	*Sansiviera trifasciata*	Snake plant	Leaves	Asparagaceae	WM-S-051	Maceration-Ethanol 96%
7	*Smallanthus sonchifolius*	Yacon	Leaves	Asteraceae	WM-S-052	Maceration-Ethanol 96%
8	*Phaseolus vulgaris*	Bean	Fructus	Fabaceae	WM-P-006	Maceration-Ethanol 96%
9	*Mikania scandens*	Climbing hempvine	Leaves	Asteraceae	WM-M-009	Maceration-Ethanol 96%
10	*Emilia sonchifolia*	Lilac tassel flower	Aerial part	Asteraceae	WM-E-023	Maceration-Ethanol 96%
11	*Lopholaena coriifolia*	Leather-leaved Fluff-bush	Aerial part	Asteraceae	WM-L-012	Maceration-Ethanol 96%
12	*Crassocephalum crepidiodes*	Fireweed	Leaves	Asteraceae	WM-C-008	Maceration-Ethanol 96%
13	*Synedrella nodiflora*	Cinderella weed	Leaves	Asteraceae	WM-S-053	Maceration-Ethanol 96%
14	*Chromolaena odorata*	Siam weed	Leaves	Asteraceae	WM-C-009	Maceration-Ethanol 96%
15	*Camellia sinensis*	Tea plant	Leaves	Theaceae	WM-C-010	Maceration – Ethanol:Water (70:30)
16	*Piper betle*	Betel pepper	Leaves	Piperaceae	WM-P-007	Maceration – Ethanol:Water (70:30)
17	*Guazuma ulmifolia*	West indian elm	Leaves	Sterculiaceae	WM-P-007	Maceration – Ethanol:Water (70:30)
18	*Aloe vera*	Aloe	Leaves	Asphodelaceae	WM-A-127	Maceration – Ethanol:Water (70:30)
19	*Murraya paniculata*	Orange jasmine	Leaves	Myrtaceae	WM-M-010	Maceration – Ethanol:Water (70:30)
20	*Rheum palmatum*	Turkish rhubarb	Root	Polygonaceae	WM-R-034	Maceration – Ethanol:Water (70:30)
21	Tamarindus indica	Tamarind	Pulp	Leguminosae	WM-T-005	Maceration – Ethanol:Water (70:30)
22	*Cassia angustifolia*	Senna	Leaves	Fabaceae	WM-C-011	Maceration – Ethanol:Water (70:30)
23	*Psidium guajava*	Guava	Leaves	Myrtaceae	WM-P-008	Maceration-Ethanol 96%
24	*Syzygium polyanthum*	Bay leaves	Leaves	Myrtaceae	WM-S-054	Maceration-Ethanol 96%
25	*Lycium barbarum*	Chinese wolfberry	Fruits	Solanaceae	WM-L-013	Maceration-Ethanol 96%
26	*Cordyline fruticosa*	Ti plant	Leaves	Asparagaceae	WM-C-012	Maceration-Ethanol 96%

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Table 1. The list of the plants, part of used, specimen numbers and the extraction method (Continued)

No	Plants	Common Name	Part of used	Family	Specimen Number	Extraction Method
27	*Clerodendrum serratum*	Bag plant	Leaves	Verbenaceae	WM-C-013	Maceration-Ethanol 96%
28	*Curcuma domestica*	Tumeric	Rhizome	Zingiberaceae	WM-C-014	Maceration-Ethanol 96%
29	*Piper cubeba*	Tailed pepper	Leaves	Piperaceae	WM-P-009	Maceration-Ethanol 96%
30	*Pluchea indica*	Indian camphorweed	Leaves	Asteraceae	WM-P-010	Maceration-Ethanol 96%
31	*Phyllanthus niruri*	Gale of the wind	Aerial part	Euphorbiaceae	WM-P-011	Maceration-Ethanol 96%
32	*Peperomia pellucida*	Pepper elder	Aerial part	Piperaceae	WM-P-012	Maceration-Ethanol 96%
33	*Elephantophus scaber*	Elephant's foot	Leaves	Asteraceae	WM-E-024	Maceration-Ethanol 96%

Table 2. Total phenolic content (TPC), total flavonoid content (TFC), antioxidant activity and anti-cholinesterase activity

No	Samples	TPC (mg/mL)	TFC (mg/mL)	FRAP Value[1]	% IC_{50}[2]
1	*Persea americana*	3.79 ± 0.06	2.82 ± 0.05	43.26 ± 0.05	4.11 ± 0.13
2	*Muntingia calabura*	5.57 ± 0.09	3.22 ± 0.12	14.04 ± 0.06	n.d
3	*Acalypha indica*	4.15 ± 0.11	3.01 ± 0.06	15.23 ± 0.09	n.d
4	*Anredera cordifolia*	2.10 ± 0.06	2.27 ± 0.20	n.d	n.d
5	*Mangifera indica*	5.51 ± 0.17	2.61 ± 0.06	14.53 ± 0.11	n.d
6	*Sansiviera trifasciata*	1.96 ± 0.04	2.57 ± 0.03	n.d	n.d
7	*Smallanthus sonchifolius*	2.21 ± 0.05	2.84 ± 0.05	15.37 ± 0.05	n.d
8	*Phaseolus vulgaris*	1.35 ± 0.01	1.43 ± 0.28	114.77 ± 0.24	n.d
9	*Mikania scandens*	3.69 ± 0.12	2.77 ± 0.04	24.29 ± 0.03	69.18 ± 0.09
10	*Emilia sonchifolia*	3.40 ± 0.06	2.90 ± 0.04	17.81 ± 0.04	n.d
11	*Lopholaena coriifolia*	1.08 ± 0.09	0.76 ± 0.17	53.07 ± 0.07	n.d
12	*Crassocephalum crepidiodes*	3.55 ± 0.13	2.72 ± 0.04	31.92 ± 0.05	n.d
13	*Synedrella nodiflora*	5.62 ± 0.14	2.79 ± 0.03	83.58 ± 0.16	n.d
14	*Chromolaena odorata*	7.70 ± 0.12	3.01 ± 0.03	16.82 ± 0.01	52.14 ± 0.05
15	*Camellia sinensis*	0.72 ± 0.07	1.06 ± 0.17	19.59 ± 0.17	n.d
16	*Piper betle*	0.04 ± 0.01	0.01 ± 0.00	n.d	n.d
17	*Guazuma ulmifolia*	0.03 ± 0.00	0.23 ± 0.07	n.d	n.d
18	*Aloe vera*	n.d	n.d	n.d	n.d
19	*Murraya paniculata*	n.d	0.03 ± 0.01	16.44 ± 0.01	n.d
20	*Rheum palmatum*	0.83 ± 0.01	0.10 ± 0.01	n.d	n.d
21	*Tamarindus indica*	0.74 ± 0.06	0.62 ± 0.01	n.d	n.d
22	*Cassia angustifolia*	1.65 ± 0.10	1.20 ± 0.17	14.85 ± 0.17	n.d
23	*Psidium guajava*	2.30 ± 0.05	1.99 ± 0.21	28.89 ± 0.21	n.d

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Table 2. Total phenolic content (TPC), total flavonoid content (TFC), antioxidant activity and anti-cholinesterase activity (Continued)

No	Samples	TPC (mg/mL)	TFC (mg/mL)	FRAP Value[1]	% IC_{50}[2]
24	*Syzygium polyanthum*	4.89 ± 0.06	2.41 ± 0.16	22.85 ± 0.09	n.d
25	*Lycium barbarum*	1.04 ± 0.03	1.45 ± 0.21	36.57 ± 0.04	91.27±0.07
26	*Cordyline fruticosa*	1.37 ± 0.04	2.25 ± 0.27	25.29 ± 0.03	n.d
27	*Clerodendrum serratum*	3.95 ± 0.01	2.82 ± 0.08	38.33 ± 0.03	n.d
28	*Curcuma domestica*	8.77 ± 0.04	3.06 ± 0.03	38.33 ± 0.05	n.d
29	*Piper cubeba*	5.50 ± 0.08	0.57 ± 0.09	10.89 ± 0.06	44.08 ± 0.14
30	*Pluchea indica*	2.90 ± 0.02	2.91 ± 0.05	15.78 ± 0.11	n.d
31	*Phyllanthus niruri*	3.77 ± 0.05	2.96 ± 0.02	13.16 ± 0.06	76.93 ± 0.08
32	*Peperomia pellucida*	1.88 ± 0.06	1.62 ± 0.24	52.65 ± 0.14	86.33 ± 0.15
33	*Elephantophus scaber*	6.08 ± 0.09	3.22 ± 0.07	25.42 ± 0.09	n.d
34	Galanthamine	-	0.11 ± 0.07	-	-
35	Quercetine	3.03 ± 0.04	-	-	-
36	Rutin	26.60 ± 0.13	-	-	-
37	Trolox	47.16 ± 0.09	-	-	-
38	Ascorbic Acid	1.00 ± 0.03	-	-	-

n.d: not determined. Data were acquired from three data-independent experiments, represented in value ±SD, each performed in three replicates (n = 9).

[1] FRAP value represents the concentration of samples that have an absorbance value equal to that of 1 mM Fe_2SO_4.

[2] IC_{50} was the concentration of the sample that gives 50% inhibition of acetylcholinesterase

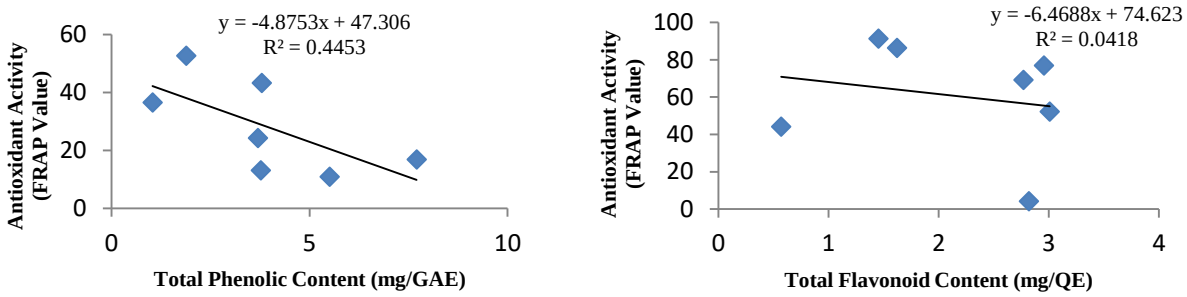

Figure 1. Correlation between (1) Total Phenolic Content and Antioxidant Activity (left); (2) Total Flavonoid Content and Antioxidant Activity (right)

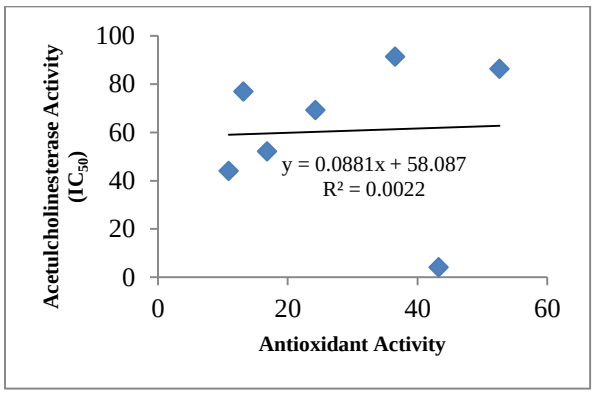

Figure 2. Correlation between Antioxidant Activity and Acetylcholinesterase Activity

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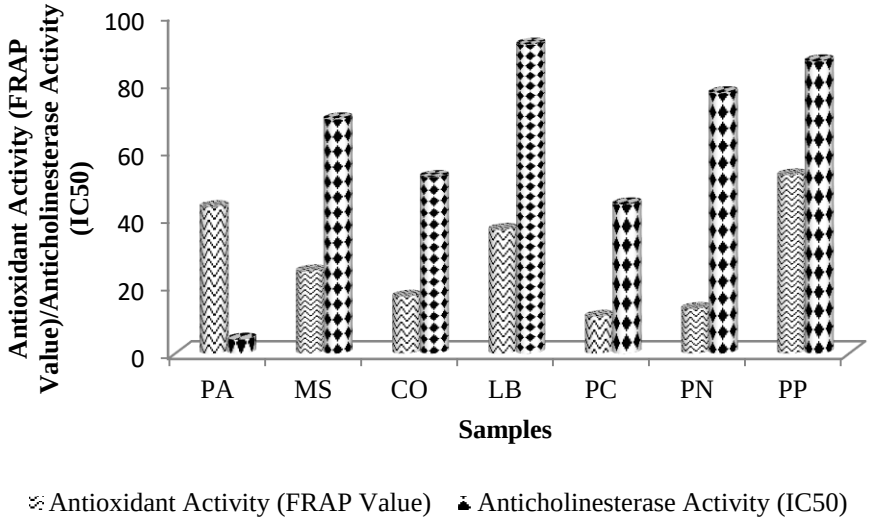

Figure 3. Comparison between Plant samples that have Acetylcholine esterase activity vs their Antioxidant activity (PA: *Persea americana*; MS: *Mikania scandens*; CO: *Chromolaena odorata*; LB: *Lycium barbarum*; PC: *Piper cubeba*; PN: *Phyllanthus niruri*; PP: *Peperomia pellucida*)

4. Discussion

4.1. Acetylcholinestrase inhibitory activity

Medicinal plants are widely known to play many roles in maintaining health and treating diseases in many countries. More than 200 plants (from 70 families) are estimated to be used for neurodegenerative diseases. Species from the Fabaceae, Asteraceae, and Lamiaceae families were recorded as the most contributing to this activity [24]. Ellman method was used in this research to measure acetylcholinesterase potency from 33 plants that are usually used for traditional medicines in Indonesia. The mechanism of this method is based on the ability of the sample to hydrolyze *β*-naphthyl acetate into naphthol and acetate, where naphthol reacts with fast blue B salts to produce a purple color. From 33 plants, there are only seven plants that give acetyl cholinesterase activity (Table 2), there are two plants from Asteraceae family (*Chromolaena odorata* (CO) and *Mikania scandes* (MS)), two plants from Piperaceae (*Piper cubeba* (PC) and *Peperomia pellucida* (PP)), and the others from Lauraceae (*Persea americana* (PA)), Solanaceae (*Lycium barbarum* (LB)) and Euphorbiaceae (*Phyllanthus niruri* (PN)). The sequences from the highest activity to low activity were PA>PC>CO>MS>PN>PP>LB with the IC_{50} range to 4.1099 – 91.2688 mg/mL, respectively.

Asteraceae is one of the most prominent plant families, consisting of approximately 1700 genera with more than 24,000 species. Almost all species from this family are spread worldwide, including in Indonesia [32]. Plants from this family are being used to treat various diseases, including neurodegenerative diseases. *Silybum marianum, Phagnalon saxatile, Pulicaria stephanocarpa, Calendula officinalis, Chamaemelum nobile*, and *Artemisia annua* proved to inhibit AChE [3, 33-35].

Phenolic, essential oil and terpenoids are active compounds thought to have the potential to inhibit the action of acetylcholinesterase [33, 36, 37]. Plants from the Piperaceae family, such as *Piper cubeba* and *Peperomia pellucida*, have been proven to inhibit acetylcholinesterase. Previous research reported five essential oils (EO) obtained from Piper species in inhibiting

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acetylcholinesterase (AChE) with IC_{50} values range of 1.51 - 14.0 mg/mL(6). Major constituents of EO piper are caryophyllene (sesquiterpenes) and asaricin (phenylpropanoids), which are also contained in *Piper cubeba* and *Peperomia pellucida*(38,39). Piperine, piperettine, piperettyline, bavinol A, ampelopsin, and violanthin isolated from Piper species also exhibited AChE inhibitory properties(3,40–43).

Phyllanthus niruri is one of the plants belonging to the Euphorbiaceae Family. Several species belonging to this family have been investigated for the potential to inhibit acetylcholinesterase. *Jatropha gossypifolia* (leaves, stem bark, and roots), extracted in different solvents, showed that the ethyl acetate of leaf extracts exhibited the highest AChE with a value of 80.46 ± 0.44%. Another study reported that *Croton socotranus* leaves and flowers extracted with ethanol showed inhibition of AChE. Another plant, *Phyllanthus acidus* (methanol extract), was reported to inhibit AChE with an IC_{50} value of 449.51 µg/mL(3,44–46). Diterpenoid isolated from *Euphoria fischeriana* and 4-O-methyl gallic acid from *Euphorbia schimperiana* and *Euphorbia balsamifera* are some of the promising AChE inhibitors(47,48). Previous research reported that *Persea americana* has potential as an AChEI. In this study, the parts used were leaves and seeds, where the inhibitory activity of seeds was higher when compared to leaf extract. This research also stated that secondary metabolites that play a role in this inhibitory process are saponins, alkaloids, and terpenoids. In our finding, ethanol extract of *Persea americana* (Lauraceae) inhibits the greatest activity for acetylcholinesterase compared to other plants. Another researcher stated that isolated alkaloids from three Cryptocarya species, which belong to this family, can inhibit AChE. In a separate study, *Beilschmiedia pulverulenta* essential oils exhibited inhibition of around 56.5% against AChE [49]. Much research in this decade concluded that alkaloids are the most potent secondary metabolites for AChE inhibitors, and one of the families containing most alkaloids is Solanaceae. Several experiments have reported alkaloids such as indole alkaloid (uleine) and isoquinoline alkaloid as cholinesterase inhibitors [50, 51]. *Lycium barbarum*, one of the plants belonging to the Solanaceae family, exhibits weaker AChE inhibitors compared to other plants in this research. This potency is probably due to less alkaloid content in the fruits compared to the leaves [52, 53].

4.2. Antioxidant Activity

The antioxidant activity was evaluated using the FRAP method. The results (Table 2) disclose that *Piper cubeba* has the highest antioxidant activity with the FRAP Value of 4.11 mg/mL, which is even better than standard Rutin and Trolox. The order of antioxidant activity for plants that have activity as AChEI was PC>PN>CO>MS>LB>PA>PP with the range of value 4.11 – 52.65 mg/mL. According to Muchandi *et al*. (2018), the antioxidant potency of the plants used for this research indicates potent antioxidant action [54]. Literature study states that almost all plants have antioxidant potency due to the plant's activity in facing photo-oxidative stress [55]. Oxidative chain reaction termination, free radical scavenging, pro-oxidant metal ions binding, and reducing capacity are believed to be involved in the antioxidant capacity of plant extracts [56]. The active substances involved in antioxidant action were phenolic compounds, including flavonoids and tannins, and some alkaloids. The antioxidant capacity of polyphenols is due to their ability to

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bind ions that trigger the formation of reactive oxygen species [57]. Existing research shows that flavonoids not only function as antioxidants by capturing free radicals or activating the secretion of superoxide dismutase and glutathione but can also contribute to treating neurodegenerative diseases [58]. Through research by Cui et al. (2020), catechin tannins and their derivatives can be used to treat neurodegenerative diseases, where this ability is related to the way and position of the binding of the hydroxyl group [58]. In this research no correlation between total phenolic content/total flavonoid content and antioxidant activity (Figure 1). Alkaloids are strong antioxidants; some of the alkaloids, such as caffeine and nicotine, have already been proved to protect neurons from oxidative stress and prevent memory loss [58, 59].

4.3. The correlation between Antioxidant Activity and Acetyl cholinesterase Activity

It has been observed in the brain of AD patients that the presence of oxidative stress and the amount of Cu2+ and Fe2+ gradually increase [16]. This condition indicated that metal accumulation can trigger AD's emergence [60]. Due to the large number of free radical products in the brains of AD patients, antioxidants are considered effective in treating this disease [4, 61]. Phenolic and flavonoid compounds are well known for their great antioxidant activities, and this activity is due to their potency to scavenge free radicals or chelating metal ions [35, 60, 62]. Despite their antioxidant abilities, the phenylchroman backbone served as the minimum structural requirement for phenol to inhibit AChE, and their specific structure can influence their inhibition strength [4]. Flavonoids have been well-known as powerful antioxidants that can reduce oxidative stress in AD patients [4]. This ability is attributed to the presence of an –OH group on the side phenyl ring of the compound [16]. Unsaturation of the C-ring number and position of hydroxyl groups, especially A5-OH, A6-OH, and A7-OH, determine the potential of flavonoids as AChEI [4, 63-65]. AChEI flavonoids are concluded to have several mechanisms of action: (1) increasing nerve transmission [64, 66]; (2) increasing the amount of acetylcholine [67]; (3) inhibition of acetylcholine hydrolysis [19]. However, the efficacy of phenolic and flavonoids as AChE inhibitor agents would depend on their bio accessibility and bioavailability since most of them are hydrophilic substances. This condition might also be one of the reasons that there is no correlation between antioxidant activity and anticholinesterase inhibitor activity (Figures 1 & 2) in this research. This fact is also supported by data showing that plants with high antioxidant activity do not always have good acetylcholine inhibitory activity (Figure 3). Even though research may not correlate terpenoids with their antioxidant activity, there is a straight relationship between monoterpenoid structure and their AChE inhibitory potency. The position of the double bond of allylic methyl group - bicyclic monoterpene hydrocarbon influences their AChEI activity [64, 65]. Since Acetylcholinesterase takes an important role in AD and has even proven to have the potency to lower stroke risk [66], the importance of continuing the research to find out the active compounds from 7 plants that have the potential as an AChEI becomes the next step project.

5. Conclusion

The research results showed that of the 33 traditional medicinal plants generally used in Indonesia, seven plants were found to have acetylcholinesterase inhibitory activity. Of these seven plants, *Persea americana* proved to have higher AChEI activity, while *Piper cubeba* had

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the highest antioxidant activity. The statistical results showed no correlation between acetylcholinesterase inhibitor activity and antioxidant potency.

Author contributions

All authors have the same contribution in conducting literature studies, research and journal writing.

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Conflict of interest

The authors declare no conflict of interest.

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