Pharmacogn J. 2020; 12(6): 1429-1439
A Multifaceted Journal in the field of Natural Products and Pharmacognosy
www.phcogj.com

Research Article

Southeast Asian Medicinal Plants with Angiotensin Converting Enzyme (ACE) Inhibition Properties

T. A. Faiz T. Anuar[1], Azlini Ismail[2,*]

ABSTRACT

Introduction: This article aims to provide a summary of medicinal plants in the Southeast Asian countries that have an angiotensin-converting enzyme (ACE) inhibitory activity that is therapeutically useful for treating hypertension. **Methods:** This review paper is a result of extensive searches via electronic database platforms, including Pubmed, Google Scholar, Scopus, and Science Direct with the keyword search terms: ACE enzyme, Southeast Asia countries, plants, and extracts. **Results:** Thirty-four articles on ACE inhibition activity of 76 Southeast Asian medicinal plants were found and further reviewed. Several plants from Malaysia (*Chassalia curviflora, Citrus hystrix, Murraya koenigii, Senna garrettiana*), Indonesia (*Gnetum Gnemon, Momordica charantia, Nasturtium officinale, Peperomia pellucida, Pereskia saccharose*), and Thailand (*Mammea siamensis*) were found to exhibit strong ACE inhibitory activity *in vitro*. Bioactive compounds such as 3′,4′, dihydroxy-3-5 dimethoxy flavone-7-O-β-rhamnose and quercetin-3-O-glucoside showed the highest potency in exhibiting the ACE inhibition activity in this review. **Conclusions:** This review suggests for an in-depth investigation on the potent crude extracts for the potential development of complementary herbal medicines as well as on the potent ACE inhibitor compounds for further development as new ACE inhibitor candidates for hypertension therapy.

Key words: ACE, Angiotensin-converting enzyme, Antihypertensive, Medicinal plants, Southeast Asia.

T. A. Faiz T. Anuar[1], Azlini Ismail[2,*]

[1]Department of Chemistry, Kulliyyah of Science, International Islamic University Malaysia, 25200 Kuantan, Pahang, MALAYSIA.
[2]Department of Fundamental Dental and Medical Sciences, Kulliyyah of Dentistry, International Islamic University Malaysia, 25200 Kuantan, Pahang, MALAYSIA.

Correspondence

Azlini Ismail

Department of Fundamental Dental and Medical Sciences, Kulliyyah of Dentistry, International Islamic University Malaysia, 25200 Kuantan, Pahang, MALAYSIA.

E-mail: dr_azlini@iium.edu.my

History

- Submission Date: 21-06-2020;
- Review completed: 02-08-2020;
- Accepted Date: 10-08-2020.

DOI : 10.5530/pj.2020.12.197

Article Available online

http://www.phcogj.com/v12/i6

KEY MESSAGE

This review paper aims to provide an extensive review of traditional medicinal plants found in Southeast Asia region with inhibition activity against ACE enzyme as an insight for the potential discovery of new antihypertensive drugs.

INTRODUCTION

Hypertension has become one of the global health problems in this decade. Hypertension is a condition of high blood pressure that occurs when the arteriolar resistance increases within blood vessels resulted from the increased peripheral arteriolar smooth muscle tone.[1] There was a massive increase from 594 million of hypertension cases in 1975 to 1.13 billion of cases in 2015 throughout the world.[2] In Malaysia alone, the prevalence of hypertension for this decade (2010-2017) seems to be stagnantly high with the prevalence of 29.2 % when compared to previous decade's prevalence (2000-2010) with the value of 28.7 %.[3]

In the human body, blood pressure is controlled by two overlapping mechanisms, the baroreflexes and the renin-angiotensin-aldoesterone system (RAAS). RAAS involves several organs releasing enzymes including the kidney that releases renin which is also known as angiotensinogenase. Renin is synthesized mainly in the juxta-glomerular apparatus and is secreted into the circulation in response to hypotension and hypernatremia.[4] Renin will act on circulating angiotensinogen by cleaving the N-terminal segment of angiotensinogen to form the biologically inert decapeptide hormone, the angiotensin I (Asp-Arg-Val-Tyr-Ile-His-Pro-Phe-His-Leu). Angiotensin converting enzyme (ACE) which is a zinc ion-dependent dipeptidyl carboxypeptidase then hydrolyzes angiotensin I by cleaving the carboxyl terminal His-Leu dipeptide to form the active octapeptide angiotensin II (Asp-Arg-Val-Tyr-Ile-His-Pro-Phe). The binding of angiotensin II to angiotensin II type 1 (AT1) receptor causes contraction of vascular smooth muscle cells leading to increased vascular resistance, and it also stimulates the production of aldosterone in the adrenal cortex which in turn increases renal sodium resorption and potassium secretion.[5] Blocking the ACE enzyme reduces the formation of angiotensin II; increases the number of bradykinin, an endothelium-dependent vasodilator; and also reduces aldosterone secretion, all these lead to a reduction in blood pressure[1,6] and have contributed to the clinical use of ACE inhibitors in managing hypertension.

Captopril, the prototype ACE inhibitor drug was first developed by employing quantitative structure activity-based modifications following the finding on one of the peptides (bradykinin-potentiating factor) from the venom of Brazilian lancehead viper *Bothrops jararaca* that can inhibit the conversion of angiotensin I into angiotensin II by inhibiting the ACE activity.[7] Captopril was then approved by Federal Drug Administration for oral use, and currently, there are several subclasses of ACE inhibitors which include sulfhydryl (-SH) containing

Cite this article: Anuar TAFT, Ismail A. Southeast Asian Medicinal Plants with Angiotensin Converting Enzyme (ACE) Inhibition Properties. Pharmacogn J. 2020;12(6):1429-39.

analogs, carboxyl (-COOH) containing analogs, phosphoryl (-PO_2) containing analogs, hydroxamic non-amino acid derivatives, peptides and peptidomimetics with different potencies depending on their affinity towards the zinc-binding site on the ACE.[8]

Despite the therapeutic benefits of ACE inhibitors, sulfhydryl (-SH) containing analogs lead to many side effects including skin rash and taste sense impairment because of its sulfhydryl component presence; this has led to the development of non-sulphur captopril analogs such as enalapril and lisinopril.[9] However, there are also several other adverse effects commonly found in patients on ACE inhibitors including of persistent dry cough, low blood pressure (in hypovolemic states), hyperkalemia and in some cases, angioedema which results from an increased bradykinin level, as well as malformation of fetus if taken by the pregnant woman.[1] Despite the emergence of angiotensin-receptor blockers (ARB) as an alternative drug choice with less of these side effects, ACE inhibitors were more protective in the advancement and hospitalization of the hypertensive patient for heart failure as compared to ARB.[10] Thus, the use of ACE inhibitors remains relevant in the current practice of managing hypertension.

Henceforth, studies exploring the new effective ACE inhibitor drug with fewer side effects are continually emerging. Bioactive peptides from marine organisms like fish, shellfish, seaweed, microalgae, molluscs; the food proteins such as milk, ovalbumin, turtle eggs, cheese, chicken eggs, casein; and some plant-derived peptides extracted from legumes, corn, bitter melon seeds, algae, mushrooms have shown very promising ACE inhibition activities.[11] Despite so, there are also some extracted bioactive compounds from various phytochemical groups in medicinal plants such as hydrolysable tannins, phenylpropanes, proanthocyanidins, flavonoids, xanthones, fatty acids, terpenoids, alkaloids, oligosaccharides and peptide amino acids were identified to have ACE inhibitory activity.[12] Nonetheless, this review paper focuses on bioprospecting the medicinal plants with the ACE inhibition activity.

Currently, few review papers have compiled the medicinal plants with ACE inhibition activities from all over the world [7,13-15], however, none of these papers focused on the medicinal plants from Southeast Asia region. Southeast Asia region is rich with underexplored medicinal plants. In this region, at least 2,200 medicinal and poisonous plants recorded in the literature in which they wildly inhabit open spaces (59 %) and forest (31 %) or they are cultivated (10 %). The studied medicinal plants are usually the ones that are commonly found in the open, disturbed space; on the other hand, plants that inhabit forest may be largely left unexplored. The huge remaining forest land in the Southeast Asia region becomes a vast reservoir for plant-derived drug discovery.[16] Hitherto, this study aims to provide an extensive review of traditional medicinal plants found in Southeast Asia region with inhibition activity against ACE enzyme as an insight for the new potential discovery of antihypertensive drug.

METHODOLOGY

The bibliographic search was performed in the following databases: PubMed, Google Scholar, Scopus, and Science-Direct. These databases were searched for relevant studies which include at least one of the following keywords: (i) Angiotensin converting enzyme, (ii) Southeast Asia countries specifically Malaysia, Indonesia, Thailand, Singapore, Brunei, Vietnam, Philippines, Laos, and also Myanmar, (iii) plants and (iv) extract. Only articles that met the following conditions were included: i) Articles on ACE inhibition studies of crude extracts, fractions, and isolated compounds of plants, thus, studies related to protein or peptides activity on ACE inhibition were omitted, and ii) Articles include ACE inhibition studies on plants that were commonly found in the Southeast Asian countries. No limit was placed on the search time frame to retrieve all relevant papers, and the last search was performed on April 6, 2020. About 34 papers with 76 medicinal plants have been reviewed including journal articles and proceedings.

TREND OF ACE INHIBITION STUDIES ON SOUTHEAST ASIAN MEDICINAL PLANTS

There are 76 medicinal plants across Southeast Asia with ACE inhibition activity found from studies dated back from the year 2007 until recently (Table 1). This review will discuss in terms of distribution of the plants across Southeast Asia region, the assay methods and the efficacy of plant extracts, fractions as well as bioactive compounds.

Distribution of Plants

At least 76 plants in the Southeast Asia region that has proven ACE inhibition activity (Figure 1). The majority of these studies were from Indonesia with 35 plants, contributing about 44 % of the whole studies. Following afterward Indonesia, 28 plants were from Malaysia which accounts for 37 %; nine plants were from the Philippines which accounts for 11 %; six plants were from Thailand with 7 % and the least number of studies with two plants were from Vietnam which accounts for 3 % of total studies. Since the hot and humid climate around Southeast Asia is quite similar especially at the islands of Indonesia, Philippines, and Malaysia, several plants exist across the Southeast Asia region, and are not confined in only one country. For example, *Morus alba* Lin. are studied in both countries Indonesia[19] and Philippines[20]. *Gynura procumbens*[23,29] and *Orthosiphon stamineus* Benth[19, 37] were also studied in both Malaysia and Indonesia while *Apium graveolens* L was studied in Thailand[18] and Indonesia[19].

Extraction procedures

The extraction method indeed plays a massive role in obtaining the desired active compound. Extraction is a process of separating plant tissue portions that are medicinally active by utilizing standard procedures by specific solvents.[47] There are various extraction procedures adopted in the ACE inhibition studies across the Southeast Asia region; these include the commonly-used extraction methods such as maceration, infusion, decoction, and also the less-common methods such as the centrifugation and assisted-conventional methods, for instance, the microwave-assisted and also ultrasound-assisted extraction methods.

In this review, the centrifugation method was not commonly being employed except for studies involving grey oyster mushrooms[42] and

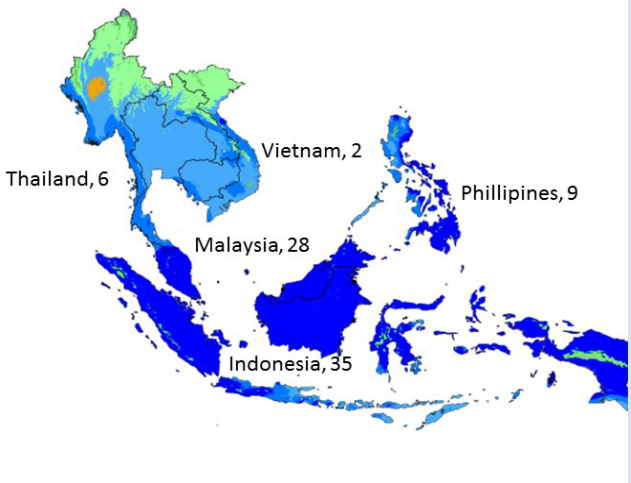


Figure 1: ACE inhibition studies on medicinal plants across Southeast Asia.

Table 1: Medicinal Plants in Southeast Asia region with the property of inhibiting angiotensin-converting enzyme (ACE).

Scientific name	Part of plants	Type of extraction	Solvent used	Plants origin	ACE inhibitory activity (%)	IC_{50} (µg/ml)	Reference
Agrocybe sp.	Fruiting bodies	Infusion	Distilled water	Malaysia	NA	890 ± 0.05	[17]
Anacardium occidentale Linn.	Leaves	Reflux	Ethyl acetate	Thailand	64.20	NA	[18]
Andrographis paniculata (Burm.f.) Ness.	Herbs	Maceration	Ethanol 95%	Indonesia	29.38 ± 1.82	NA	[19]
Annona muricata L.	Leaves	Maceration	Ethanol 95%	Indonesia	5.57 ± 2.10	NA	[19]
Apium graveolens L.	Leaves	Maceration	Ethanol 95%	Indonesia	37.91 ± 5.67	NA	[19]
	Whole plants	Reflux	Methanol	Thailand	82.30	1,700.00	[18]
Artocarpus heterophyllus	Leaves	Maceration	Methanol	Philippines	43.00	NA	[20]
	Leaves	Maceration	Methanol - hexane	Philippines	40.00	NA	[20]
	Leaves	Maceration	Methanol – ethyl acetate	Philippines	47.00	NA	[20]
Auricularia auricular-judae	Fruiting bodies	Infusion	Distilled water	Malaysia	NA	510.00 ± 0.02	[17]
Averrhoa bilimbi L.	Leaves	Maceration	Ethanol 95%	Indonesia	71.48 ± 1.71	NA	[19]
Blumea balsamifera	Leaves	Fabricated tea bags – air dried	Water	Philippines	211.30	NA	[21]
		Fabricated tea bags – oven dried	Water	Philippines	70.42	NA	[21]
Bixa orellana	Leaves	Maceration	Methanol	Philippines	18.00	NA	[20]
	Leaves	Maceration	Methanol - hexane	Philippines	53.00	NA	[20]
	Leaves	Maceration	Methanol – ethyl acetate	Philippines	65.00	NA	[20]
Carica papaya	Shoots	Maceration	Hexane	Malaysia	3.00	NA	[22]
	Shoots	Maceration	Dichloromethane	Malaysia	59.77	NA	[22]
Catharanthus roseus (L.) G. Don.,	Herbs	Maceration	Ethanol 95%	Indonesia	19.27 ± 5.54	NA	[19]
	Leaves	Maceration	Petroleum ether	Indonesia	NA	437.00	[23]
	Leaves	Maceration	Ethyl acetate	Indonesia	NA	1,367.00	[23]
	Leaves	Maceration	Methanol	Indonesia	NA	402.00	[23]
Centella asiatica	Leaves	Maceration	Hexane	Malaysia	48.45	NA	[22]
	Leaves	Maceration	Dichloromethane	Malaysia	38.00	NA	[22]
	Leaves	Maceration	Water	Malaysia	73.63 ± 12.00	NA	[24]
Chassalia curviflora	Leaves	Infusion	Water	Malaysia	NA	4.96	[25]
	Leaves	Maceration	Methanol	Malaysia	NA	4.06	[25]
	Flower	Infusion	Water	Malaysia	NA	3.39	[25]
	Flower	Maceration	Methanol	Malaysia	NA	3.71	[25]
Citrus hystrix	Fruits	Maceration	Water	Malaysia	90.97 ± 4.60	NA	[24]
Collybia reinakeana P. Henn	Pileus	Maceration	Hot water	Philippines	42.00	NA	[26]
	Stipe	Maceration	Hot water	Philippines	42.00	NA	[26]
Cosmos caudatus	Leaves	Maceration	water	Malaysia	88.49 ± 0.85	NA	[24]
	Whole herbs	Maceration	Hexane	Malaysia	5.00	NA	[22]
	Whole herbs	Maceration	Dichloromethane	Malaysia	51.00	NA	[22]
Curcuma longa	Rhizome	Maceration	Water	Malaysia	33.89 ± 0.96	NA	[24]
Curcuma domestica Val	Rhizome	Maceration	Ethanol 95%	Indonesia	24.15 + 3.21	NA	[19]
Cyclea barbata Miers.	Leaves	Maceration	Ethanol 95%	Indonesia	35.57 + 4.54	NA	[19]
Eleusine indica	Leaves	Maceration	Methanol – ethyl acetate	Philippines	NA	32.00	[27]
	Leaves	Maceration	Methanol	Philippines	68.84	NA	[27]
	Leaves	Maceration	Methanol - hexane	Philippines	47.00	NA	[27]
	Leaves	Maceration	Methanol – ethyl acetate	Philippines	51.51	NA	[27]
	Leaves	Maceration	Methanol - water	Philippines	41.00	NA	[27]
	Leaves	Decoction	Water	Philippines	2.00	NA	[27]
Ganoderma lucidum	Fruiting bodies	Infusion	Distilled water	Malaysia	NA	50.00 ± 0.009	[17]
Gnetum gnenom l.	Seeds	Reflux	N-hexane	Indonesia	79.28	NA	[28]
	Seeds	Reflux	Dichloromethane	Indonesia	89.92	NA	[28]
	Seeds	Reflux	Ethylacetate	Indonesia	92.10	NA	[28]
	Seeds	Reflux	Methanol	Indonesia	90.64	NA	[28]
	Seeds	Reflux	Water	Indonesia	89.90	NA	[28]
Gynandropsis gynandra	Leaves	Maceration	Water	Malaysia	35.55 ± 3.85	NA	[24]

Gynura procumbens	Whole plant	Maceration	Ethanol	Malaysia	NA	800.00	[29]
	Leaves	Maceration	Petroleum ether	Indonesia	NA	432.00	[23]
	Leaves	Maceration	Ethyl acetate	Indonesia	NA	227.00	[23]
	Leaves	Maceration	Methanol	Indonesia	NA	453.00	[23]
Hericium erinaceus	Fruiting bodies	Infusion	Distilled water	Malaysia	NA	580.00 ± 0.023	[17]
Hibiscus rosasinensis	Leaves	Maceration	Petroleum ether	Indonesia	NA	431.00	[23]
	Leaves	Maceration	Ethyl acetate	Indonesia	NA	384.00	[23]
	Leaves	Maceration	Methanol	Indonesia	NA	271.00	[23]
Mammea siamensis	Whole plants	Ultrasound-assisted extraction	Ethanol 95 %	Thailand	97.50 ± 0.20	NA	[30]
Manihot esculenta	Shoots	Maceration	Hexane	Malaysia	4.00	NA	[22]
	Shoots	Maceration	Dichloromethane	Malaysia	27.00	NA	[22]
Melia azedarach	Leaves	Maceration	Petroleum ether	Indonesia	NA	536.00	[23]
	Leaves	Maceration	Ethyl acetate	Indonesia	NA	588.00	[23]
	Leaves	Maceration	Methanol	Indonesia	NA	483.00	[23]
Mesona palustris Bl.	Leaves	Maceration	Ethanol 95 %	Indonesia	36.25 + 5.71	NA	[19]
Mesue ferrea	Whole plants	Ultrasound-assisted extraction	Ethanol 95 %	Thailand	9.73 ± 0.09	NA	[30]
Mimusops elengi	Whole plants	Ultrasound-assisted extraction	Ethanol 95 %	Thailand	9.5 ± 0.30	NA	[30]
Momordica charantia L.	Leaves	Maceration	Ethanol	Indonesia	NA	7.52	[31]
	Leaves	Maceration	Ethyl acetate fraction	Indonesia	NA	4.29	[31]
Moringa oleifera Lam	Leaves	Maceration	Methanol	Philippines	64.23 ± 0.06	NA	[32]
Morinda citrifolia L.	Leaves	Maceration	Ethanol 95%	Indonesia	66.64 + 2.32	NA	[19]
Morus alba Linn.	Leaves	Maceration	Ethanol 95%	Indonesia	46.05 + 3.07	NA	[19]
	Leaves	Maceration	Methanol	Philippines	22.00	NA	[20]
	Leaves	Maceration	Methanol - hexane	Philippines	28.00	NA	[20]
	Leaves	Maceration	Methanol- ethyl acetate	Philippines	48.00	NA	[20]
Muntingia calabura l.	Leaves	Maceration	Ethanol	Indonesia	NA	1.25	[33]
	Leaves	Maceration	Ethyl acetate fraction	Indonesia	NA	0.63	[33]
Murraya koenigii	Leaves	Maceration	Water	Malaysia	91.20 ± 4.15	NA	[24]
Myrica esculenta	Leaves	Reflux	Methanol	Vietnam	29 .97	NA	[34]
Nasturtium officinale R. Br.	Herbs	Maceration	Ethanol 95%	Indonesia	51.94 + 2.92	NA	[19]
	Herbs	Maceration	Ethanol 70 %	Indonesia	NA	19.05	[35]
	Herbs	Maceration	Ethyl acetate fraction	Indonesia	NA	2.30	[35]
Nymphaea pubescens	Leaves	Maceration	Methanol	Philippines	32.00	NA	[20]
	Leaves	Maceration	Methanol - hexane	Philippines	44.00	NA	[20]
	Leaves	Maceration	Methanol – ethyl acetate	Philippines	11.00	NA	[20]
Orthosiphon aristatus (Blume) Miq.	Leaves	Maceration	Water	Indonesia	69.20	NA	[36]
Orthosiphon stamineus Benth.	Leaves	Maceration	Ethanol 95%	Indonesia	55.41 ± 4.03	NA	[19]
	Leaves	Maceration	Water	Malaysia	NA	358.80 ± 24.20	[37]
	Leaves	Maceration	Ethanol 100%	Malaysia	NA	45.80 ± 1.20	[37]
	Leaves	Maceration	Methanol 100%	Malaysia	NA	63.70 ± 1.10	[37]
	Leaves	Maceration	Ethanol 50%	Malaysia	NA	58.10 ± 2.00	[37]
	Leaves	Maceration	Methanol 50%	Malaysia	NA	78.20 ± 7.90	[37]
Oxalis corniculata	Leaves	Maceration	Petroleum ether	Indonesia	NA	439.00	[23]
	Leaves	Maceration	Ethyl acetate	Indonesia	NA	325.00	[23]
	Leaves	Maceration	Methanol	Indonesia	NA	336.00	[23]
Peperomia pellucida (L.) Kunth	Herbs	Microwave-asissted extraction	Ethanol-water	Indonesia	54.73	NA	[38]
	Aerial Parts	Maceration	Methanol – ethyl acetate	Indonesia	NA	3.44	[39]
Pereskia saccharose Griseb.	Leaves	Maceration	Ethanol	Indonesia	NA	3.45	[40]
	Leaves	Maceration	Ethyl acetate	Indonesia	NA	1.71×10^{-3}	[40]
Persea americana Mill.	Leaves	Maceration	Ethanol 95%	Indonesia	29.49 ± 6.24	NA	[19]
Persea americana	Seeds	Maceration	Petroleum ether	Indonesia	NA	1,043.00	[23]
	Seeds	Maceration	Ethyl acetate	Indonesia	NA	476.00	[23]
	Seeds	Maceration	Methanol	Indonesia	NA	500.00	[23]

Phalleria marcocarpa	Leaves	Maceration	Petroleum ether	Indonesia	NA	189.00	[23]
	Leaves	Maceration	Ethyl acetate	Indonesia	NA	158.00	[23]
	Leaves	Maceration	Methanol	Indonesia	NA	102.00	[23]
	Fruits	Maceration	Petroleum ether	Indonesia	NA	162.00	[23]
	Fruits	Maceration	Ethyl acetate	Indonesia	NA	139.00	[23]
	Fruits	Maceration	Methanol	Indonesia	NA	122.00	[23]
Phyllanthus niruri L.	Herbs	Maceration	Ethanol 95%	Indonesia	13.74 ± 1.23	NA	[19]
Plantago major L	Leaves	Reflux	Methanol	Vietnam	28.06 ± 0.21	NA	[41]
Pleurotus cystidiosus	Fruiting bodies	Infusion	Distilled water	Malaysia	NA	54.00 ± 0.002	[17]
Pleurotus eryngii	Fruiting bodies	Infusion	Distilled water	Malaysia	NA	67.00 ± 0.026	[17]
Pleurotus flabellatus	Fruiting bodies	Infusion	Distilled water	Malaysia	NA	58.00 ± 0.002	[17]
Pleurotus florida	Fruiting bodies	Infusion	Distilled water	Malaysia	NA	50.00 ± 0.013	[17]
Pleurotus pulmonarius	Fresh fruiting bodies	Centrifugation	Water	Malaysia	45.80 ± 4.13	NA	[42]
	Freeze-dried fruiting bodies	Centrifugation	Water	Malaysia	29.52 ± 6.35	NA	[42]
Pleurotus sajor-caju	Fruiting Bodies	Infusion	Distilled water	Malaysia	NA	56.00 ± 0.012	[17]
Polygonum minus	Leaves	Maceration	Water	Malaysia	89.13 ± 5.42	NA	[24]
Psophocarpus tetragonolobus	Fruits	Maceration	Hexane	Malaysia	1.00	NA	[22]
	Fruits	Maceration	Dichloromethane	Malaysia	51.00	NA	[22]
Ruellia tuberosa L.	Leaves	NA	Ethanol	Indonesia	NA	55.36	[43]
Sargassum siliquosum	Whole plant	Centrifugation	Crude extract	Malaysia	NA	420.00 ± 0.04	[44]
	Whole plant	Centrifugation	Fucoxanthin-rich fractions	Malaysia	NA	940.00 ± 0.67	[44]
Sargassum polycystum	Whole plant	Centrifugation	Crude extract	Malaysia	NA	30.00 ± 0.01	[44]
	Whole plant	Centrifugation	Fucoxanthin-rich fractions	Malaysia	NA	1,530.00 ± 0.27	[44]
Schizophyllum commune	Fruiting Bodies	Infusion	Distilled water	Malaysia	NA	320.00 ± 0.070	[17]
Scurulla artopurpurea	Herbs	Maceration	Petroleum ether	Indonesia	NA	727.00	[23]
	Herbs	Maceration	Ethyl acetate	Indonesia	NA	322.00	[23]
	Herbs	Maceration	Methanol	Indonesia	NA	380.00	[23]
Senna garrettiana	Whole Plants	Ultrasound-assisted extraction	Ethanol 95 %	Malaysia	92.20 ± 2.07	NA	[30]
Sonchus arvensis	Leaves	Maceration	Water	Indonesia	39.67	NA	[36]
Solanum indicum Linn	Fruits	Maceration	Ethanol 95%	Indonesia	53.24 ± 2.88	NA	[19]
Solanum nigrum L.	Fruits	Maceration	Ethanol 95%	Indonesia	29.52 ± 5.95	NA	[19]
Solanum torvum Sw.	Fruits	Reflux	Methanol	Thailand	76.20	NA	[45]
	Fruits	Maceration	Methanol	Thailand	NA	1,200.00	[45]
Syzygium polyanthum (Wight) Walp	Leaves	Maceration	Ethanol 95%	Indonesia	53.37 ± 0.95	NA	[19]
Syzygium samarangense	Leaves	Maceration	Methanol	Philippines	20.00	NA	[20]
	Leaves	Maceration	Methanol - hexane	Philippines	75.00	NA	[20]
	Leaves	Maceration	Methanol – ethyl acetate	Philippines	57.00	NA	[20]
Sonchus arvensis (Linn.)	Leaves	Maceration	Ethanol 96%	Indonesia	NA	46.71	[46]
Swietenia mahogany	Seeds	Maceration	Petroleum ether	Indonesia	NA	774.00	[23]
	Seeds	Maceration	Ethyl acetate	Indonesia	NA	1,240.00	[23]
	Seeds	Maceration	Methanol	Indonesia	NA	1,132.00	[23]
Volvariella volvaceae	Fruiting bodies	Infusion	Distilled water	Malaysia	NA	760.00 ± 0.023	[17]
Zea mays	Silk	Maceration	Ethanol 95%	Indonesia	50.44 + 3.77	NA	[19]

Malaysian seaweeds.[44] Centrifugation-assisted extraction employs high rotational speeds and g-forces to separate the desired extract from impurities such as proteins and hydrocolloids that were present in the extract[42, 48, 49]. In this review, microwave-assisted extraction was only reported for extracting *Peperomia pellucida*.[38] This method utilizes microwave electromagnetic to promote solvent penetration into the matrix and to aid the partition of analytes from the sample matrix into the solvent. It is favorable to be used for extracting polar molecules and is usually limited to gallic acid, ellagic acid, quercertin, and trans-resveratrol which are stable under microwave heating.[50]

Ultrasound-assisted extraction was used in extracting some medicinal plants such as *Mammea siamensis, Mesue ferrea*, *Mimusops elengi* and *Senna garrettiana*.[30] This method involves the use of ultrasound ranging from 20 kHz to 2000 kHz to alter and disrupt the plant cell wall; facilitating the release of compounds and enhancing the transport of the solvents into the plant cells. This method reduces extraction time and solvent consumption, however, the use of ultrasound energy may trigger the formation of some free radicals.[50]

Maceration, decoction, and infusion are common extraction methods used in the studies included in this review (Table 1). Maceration is a process that involves soaking of the plant materials (coarse or powdered) in a container with any solvents, and the soaked plant materials are allowed to stand at room temperature for a certain period with frequent agitation. This process usually softens and break the plant's cell wall

to release the soluble phytochemicals. After the maceration period, the mixture is then pressed or strained by filtration. The choice of solvents will determine the type of compounds extracted from the macerated samples.[50] From the reported studies, there are distinguished methodological preferences in conducting maceration especially the temperature, period, and also solid solvent ratio. For temperature during maceration, most of these researches used room temperature[24,29] while there were also studies that conduct the maceration at a temperature of 50 °C[37] and also at high temperatures range of 80 to 90 °C using a waterbath.[26] The shortest period for maceration among these studies was two hours[26] and some studies used longer maceration period, such as 24 hours[24], 48 hours[33,35], and the longest period of maceration was 72 hours.[19, 27,45,46] As for solid-solvent ratio, several studies mentioned that the ratio of 1:10[36], 1:8[46] and also 1:5[37] were used. Little that we know, the solid-solvent ratio also plays a significant role in extracting the phytochemicals. The higher the ratio, the higher the phytochemicals extracted.[51] However, maceration have several disadvantages including of high consumption of solvent, thus increasing its operating cost and giving a negative effect to the environment.[52]

There are several other extraction methods adopted in these studies, for example is infusion. Infusion is an extraction procedure utilizing the same concept as maceration that involves soaking the plant materials in cold or hot water as the usual solvent, but for a shorter period as compared to maceration.[47,50,53] The use of water as the solvent reduces the cost and at the same time, overcomes the potential of environmental problem. Kadir & Mhd Omar[25] utilized both infusion and also maceration methods for *Chassalia curviflora* extraction. This study reported that leaves extracted using alcohol maceration have slightly better ACE inhibition activity than the leaves extracted through water infusion; while flowers extracted using the infusion method have slightly lower ACE inhibition activity than those extracted using the maceration method. The last commonly used extraction method used in this review is decoction. Decoction also applies the same concept of soaking the plant materials in a specified volume of water, but under the boiling conditions for a defined period. This extraction method is suitable for extracting heat-stable compounds, hard plants materials such as roots and barks and it usually extracted more oil-soluble compounds compared to maceration and infusion.[50]

Apart from the extracting method, the solvent in the extraction process also plays a significant role in distinguishing phytochemical compounds available in the extracts. The solvent can have high polarity, for instance, water, ethanol, methanol; semi polarity such as dimethylsulfoxide (DMSO), ethyl acetate, dichloromethane; and low polarity such as hexane and petroleum ether. For example, *Orthosiphon stamineus* when macerated using different solvents of ethanol 100 %, methanol 100 %, ethanol 50 %, and methanol 50 % lead to different ACE inhibition activity with IC_{50} values of 45.8, 63.7, 58.1, and 78.2 µg/ml, respectively.[37] This illustrates the importance of choosing the best solvent in extracting the metabolites that exhibit the most ACE inhibition activity.

Among the solvents used throughout these studies, polar solvents were more preferred as compared to the nonpolar solvents. None of these studies that utilized petroleum ether as the solvent for extraction exhibit high or moderate activity against ACE enzyme.[23] The leaves of *Hibiscus rosasinensis*, for example, showed better IC_{50} for extraction via methanol than *via* petroleum ether.[23] Meanwhile, the seeds of *Gnetum gnetum I.* at 100 µg/ml exhibited increasing percentages of ACE inhibition with increasing polarity of organic solvents utilized. Other previous studies also showed that petroleum ether was ineffective to extract the phytochemical constituents with ACE inhibitory effect.[54, 55] Thus, it can be concluded that the non-polar solvent especially petroleum ether are ineffective in extracting phytochemical constituents that exhibit ACE inhibition.

Moreover, we found that the highly significant ACE inhibition activity usually came from studies that used polar solvent like water, ethanol, and methanol. For example, a water solvent was used to extract *C. curviflora*[25], *Citrus hystrix*[24] and *Murraya koenigii*.[24] Ethanol 100 % and 95 % were used to extract *Momordica charantia*[31], *Muntingia calabura*[33], *Pereskia saccharose*[40], *Mammea siamensis*[30], and *Senna garrettiana*.[30] Methanol was also used to extract *C. curviflora*[25] and *G. gnemon*.[28] Apart from the polar solvent, plants such as *G. gnemon*[28] and *P. saccharose*[40] which were being extracted using ethyl acetate, a semi-polar solvent, also have highly significant ACE inhibition activity. However, in some studies, the IC_{50} values of plants extracted using methanol or ethanol were smaller than the IC_{50} values from plants extracted using ethyl acetate, while in some studies the results are in the opposite.[23] Hitherto, we conclude that both polar (water, ethanol and methanol) and semipolar (ethyl acetate) solvent were good options to extract phytochemical constituents that exhibit ACE inhibition activity.[52]

ACE inhibition assay methods

This review also examines the assay methods that were utilized to test the ACE inhibition activity (Table 2). It was found that the Cushman and Cheung Method was the most commonly utilized ACE inhibition assay. In this assay, substrate hippuryl-histidyl-leucine (HHL) is used as a substrate to be hydrolyzed by the ACE enzyme in order to produce hippuric acid (HA). The amount of HA formed is then measured using an Ultraviolet-Visible spectrophotometer (UV-VIS) instrument at a wavelength of 228 nm. The concentration of HA formed are proportional to the ACE inhibition activity by the inhibitor, which means that the stronger the inhibition of an extract, the lower the amount of HA being produced.[56]

Several studies employ the modified Cushman and Cheung method. The modifications include the usage of a different reagent which is benzene-sulfonyl-chloride (BSC) to develop the yellow color upon reaction between BSC and HA[57]; and also the usage of different methods of HA measurement including of microplate reader[57] or High-Performance Liquid Chromatography (HPLC).[58,59]

Apart from Cushman and Cheung method, there were also other types of ACE inhibition assays employed such as the Lam method and Holmquist method. The Lam method that utilizes 3-hydroxybutyrlglycyl-glycyl-glycine (3HB-GGG) is the latest ACE inhibition assay method. This method is more sensitive, simple, and precise relative to the conventional method. In this method, ACE acts upon 3HB-GGG to be cleaved into two compounds of Gly-Gly-Gly amino acid and 3-hydroxybutyric acid (3HB). The 3-HB is measured using F-kit. This method was further developed with the addition of water-soluble tetrazolium salt (WST1) and also flow injection analysis. This method was then patented in the kit form named ACE kit-WST1.[56] Meanwhile the Holmquist method utilizes tripeptide furanacryloyl (FA-PPG) substrate.[21] ACE reacts upon FA-PPG to form dipeptide (glycylglycine) and furanacroyl-phenylalanine amino acid which are then measured at 328 nm and 352 nm wavelength. However, these two methods were not commonly being employed yet, specifically in the Southeast region.

EFFICACY OF SOUTHEAST ASIAN MEDICINAL PLANTS ON ACE INHIBITION

ACE inhibition activities for plants' crude extracts and fractions

In terms of the efficacy of ACE inhibition activity by the plant extracts in this study, it is identified that only five medicinal plants exhibit over 90.00 % ACE inhibition activity. These plants are *Citrus hystix* (at 500 µg/ml), *Gnetum Gnemon l.* (at 100 µg/ml), *Mammea siamensis* (at 1000 µg/ml), *Murraya Koenigii* (at 500 µg/ml) and *Senna garrettiana* (at 1000

Table 2: Assay methods used in ACE inhibitory studies on Southeast Asian medicinal plants.

ACE inhibition assay method	Substrate used	Measurement method	Reference method	ACE inhibition studies using the method
Cushman and Cheung Method	HHL	HPLC, UV-VIS Spectrophotometer, Microplate Reader	[60]	[18]
			[61]	[19]
			[57]	[20]
			[59]	[22]
			[62]	[24]
			[58]	[26]
			[57]	[27]
			[63]	[30]
			[57]	[32]
			[59]	[34]
			[61]	[42]
			[64]	[17]
			[65]	[23]
			[66]	[29]
			[61]	[37]
			[67]	[39]
			[68]	[44]
			[61]	[46]
Holmquist Method	FA-PPG	UV-VIS Spectrophotometer	[69, 70]	[46]
Lam Method	3HB-GGG	Microplate reader,	ACE kit-WST (Dojindo, Japan)	[28, 31, 33, 35, 36, 40]

Note: ACE: Angiotensin converting enzyme, FA-PPG: tripeptide furanacryloyl, 3HB-GGG: 3-hydroxybutyrlglycyl-glycyl-glycine, HHL: hippuryl-histidyl-leucine , HPLC: High-Performance Liquid Chromatography, UV-VIS: Ultraviolet-visible.

Table 3: Bioactive metabolites found in the studied plants of Southeast Asia.

Plant scientific names	Compound presents	Part of plants	ACE inhibitory effect	Reference
Apium graveolens L.	Junipediol A-8-O-b-D-glucoside (**1**)	Whole plants	Good ACE inhibitory activity, with an IC_{50} of 75.6 µg/ml (210 µM)	[18]
	Isofraxidin-b-D-glucoside	Whole plants	Enhances the activity by interacting with ACE at different region from **1**.	[18]
	Roseoside	Whole plants	Enhances the activity by interacting with ACE at different region from **1**.	[18]
	Apigenin-7-O-b-D-glucoside	Whole plants	Enhances the activity by interacting with ACE at different region from **1**.	[18]
	Luteolin-7-O-b-D-glucoside	Whole plants	Enhances the activity by interacting with ACE at different region from **1**.	[18]
	Icariside D2	Whole plants	Enhances the activity by interacting with ACE at different region from **1**.	[18]
Moringa oleifera Lam	Quercetin-3-O-glucoside	Leaves	ACE inhibitory activity of 56.37 ± 0.0059 at 7 µg/ml; 59.16 ± 0.0137 % at 15 µg/ml; and 75.74 ± 0.0161 % at 28 µg/ml.	[32]
	Kaempferol-3-O-glucoside	Leaves	N/A	[32]
Myrica esculenta	Corchoionoside C	Leaves	ACE inhibitory activity of 29.97 %	[34]
	(6S,9R)-Roseoside	Leaves	ACE inhibitory activity of 25.63 %	[34]
	Myricanol	Leaves	Weak ACE inhibitory activity.	[34]
	5-Ob-D glucopyranosyl myricanol	Leaves	Weak ACE inhibitory activity.	[34]
	Myricetin	Leaves	Weak ACE inhibitory activity.	[34]
Peperomia pellucida (L.) Kunth.	3',4', Dihydroxy-3-5 dimethoxy flavone-7-O-β-rhamnose	Aerial parts	High ACE inhibitory activity with IC_{50} value of 7.72 µg/ml.	[39]

Plantago major L	10-Hydroxy-majoroside	Leaves	High ACE inhibitory activity of 28.06% at concentration of 100 µM.	[41]
	γ '-β -D-Glucopyranoside	Leaves	Weak ACE inhibitory activity.	[41]
	6-Hydroxyapigenin 7-O-beta-D-glucoside	Leaves	Weak ACE inhibitory activity.	[41]
Solanum torvum	(E)-2,3-Dihydroxycyclopentyl-3-(3′,4′ dihydroxyphenyl) acrylate	Fruits	Weak ACE inhibitory activity with IC_{50} value of 778 µg/mL.	[45]
	Lariciresinol-4,4′-O-β-D-diglucoside	Fruits	Scarcely showed any ACE inhibitory activity.	[45]
	Methyl salicylate glycoside	Fruits	Scarcely showed any ACE inhibitory activity.	[45]

µg/ml) with the ACE inhibition values of 90.97 %, 90.64 – 92.10 %, 97.50 %, 91.20 % and 92.20 % respectively. There are also plant extracts that exhibit moderate ACE inhibition activity like *Anacardium occidentale Linn.* (64.20 %), *Apium graveolens L.* (82.3 %), *Averrhoa bilimbi L.* (65.00 - 71.48 %), *Carica papaya* (59.77 %), *Centella asiatica* (73.63 %), *Cosmos caudatus* (51.00 - 88.49 %), *Eleusine indica* (68.84 %), *Moringa oleifera Lam* (64.23 %), *Morinda citrifolia L.* (66.64 %), *Nasturtium officinale R. Br.* (51.94 %), *Orthosiphon aristatus (Blume) Miq.* (69.20 %), *Orthosipon stamineus Benth.* (55.41 %), *Peperomia pellucida (L.) Kunth* (54.73 %), *Polygonum minus* (89.13 %), *Psophocarpus tetragonolobus* (51 %), *Solanum indicum Linn* (53.24 %), *Solanum torvum Sw.* (76.20 %) *Syzygium polyanthum (Wight) Walp* (53.37 – 75.00 %) and also *Zea mays* (50.44 %).

Several plants have more than one value of percentage inhibition activity as differents studies were reported on the same plant, for example for *C. Caudatus* with the ACE inhibition values of 51.00 %[22] and also 88.49 %[24]; *S. polyanthum (Wight) Walp* with the ACE inhibition values of 53.37 %[19] and 75.00 % [20]; and also *A. bilimbi L.* with the ACE inhibition values of 65.00 % [20], 70.42 %[18 21] and 71.48 %.[19] These discrepancies between the percent of ACE inhibition activities of the same plant might derive from different extraction protocols, varying geographical location of the plant, and also seasonal variation during the plant collection period. In addition, it is also difficult to compare the efficacy between these plants using the percentage of ACE inhibition since most plant extracts were tested at different concentrations.

Another means of comparing the effectiveness of the ACE inhibition activity is by comparing the inhibitory concentration of plant extract that can inhibit 50 percent of the ACE enzyme activity. This concept is termed as IC_{50}, a usual measure of the potency of any drugs or any potential drug candidates. For instance, the lower the IC_{50}, the more potent the drug. Twenty-eight medicinal plants in this review paper have reported the plant's IC_{50} values. Among these plants, six plants were identified as highly potent, indicated by a very low IC_{50} which was lower than 10 µg/ml. These plants are *Chassalia curviflora*[25], *Momordica charantia L.*[31], *Muntingia calabura L.*[33], *Nasturtium officinale R. Br.*[35], *Pereskia saccharose Griseb*[40] and *Peperomia pellucida (L.) Kunth.*[39]

C. curviflora leaves and flower exhibited ACE inhibition activity with IC_{50} values of 4.96 µg/ml for water leaves extract, 4.06 µg/ml for methanol leaves extract, 3.39 µg/ml for water flower extract, and 3.71 µg/ml for methanol flower extract.[25] For *M. charantia L.*, both its ethanol crude extract and ethyl acetate fraction exhibited low IC_{50} values of 7.54 µg/ml and 4.29 µg/ml respectively.[31] The same goes for *M. calabura L.*, both its ethanol crude extract and ethyl acetate fraction also showed low IC_{50} values of 1.25 µg/ml and 0.63 µg/ml respectively.[33] In addition to that, *N. Officinale R. Br.* ethanol crude extract exhibited an IC_{50} value of 19.05 µg/ml, but its ethyl acetate fraction showed a much lower IC_{50} value of 2.30 µg/ml.[35] These studies indicated that the ethyl acetate fraction of these plants exhibited higher ACE inhibition than the crude ethanolic extract. As for *P. saccharose Griseb*, both its ethanol and ethyl acetate crude extracts illustrated high potency with IC_{50} values of 3.448 µg/ml and 1.714 x 10^{-3} µg/ml respectively.[40] Lastly, the *P. pellucida (L.) Kunth* ethyl acetate fraction has an IC_{50} value of 3.44 µg/ml.[39]

There are also other plants with significant ACE inhibition activity with reported IC_{50} values from 10 µg/ml to 100 µg/ml. These include *G. lucidum*[17], *N. officinale* [35], *P. cystidiosus*[17], *P. eryngii*[17], *P. flabellatus*[17], *P. florida*[17], *P. sajor-caju*[17], *R. tuberosa*[43], *S. polycystum*[44], and *S. arvensis*[46] with IC_{50} values of 50.00, 19.05, 54.00, 67.00, 58.00, 50.00, 56.00, 55.36, 30.00 and 46.71 µg/ml respectively.

Bioactive compounds from Southeast Asian medicinal plants with ACE inhibition activities

Apart from studies on plant crude extracts, there are several bioactive compounds with ACE inhibition activity found from six Southeast Asian medicinal plants such as *Apium graveolens L.*[18], *Moringa oleifera Lam*[32], *Myrica esculenta* [34], *Peperomia pellucida (L.) Kunth*[39], *Plantago major L*[41], and *Solanum torvum*[45]. The crude extract of *S. torvum* studied by Simaratanamongkol *et al.*[18] showed moderate inhibition against ACE enzyme at the concentration of 5 mg/ml. Although the IC_{50} of the crude extract did not show a potent inhibition (1,200 µg/ml), the isolated bioactive compound, (E)-2,3-dihydroxycyclopentyl-3-(3′,4′ dihydroxyphenyl) acrylate, showed a lower IC_{50} than the crude extract with an IC_{50} value of 778 µg/ml, indicative for a higher potency than the crude extract.[18,45]

As for *Plantago major* L, Nhiem *et al.*[41] tested eight isolated compounds and they found that only one compound, 10-hydroxy-majoroside have the highest percentage of ACE inhibition with 28.06 %; two compounds showed a very weak activity below than 3 %, and the other compounds did not show any ACE inhibition activity at all, at the tested concentration of 100 µM. *Peperomia pellucida* showed significant ACE inhibition activity with an IC_{50} value of 3.44 µg/ml, meanwhile, its flavonoid compound, 3',4', dihydroxy-3-5 dimethoxy flavone-7-O-β-rhamnose with an IC_{50} value of 7.72 µg/ml was less potent than the crude extract.[39] For *Myrica esculenta*, several metabolites have been isolated but only corchoionoside C and roseoside showed the most significant ACE inhibition activity with the value of 29.97 % and 25.30 % at a concentration of 100 µM.[34]

As for *Moringa oleifera*, its active fraction at 12 µg/ml exhibited ACE inhibition activity with the highest percentage of 95.85 ± 0.0181%, higher than the ACE inhibition value of crude extract of ethyl acetate fraction with 64.23 ± 0.0562 % at an unspecified concentration.[32] After

purification of this fraction into two compounds (the quercetin-3-O-glucoside and kaempferol-3-O-glucoside), the quercetin-3-O-glucoside exhibited ACE inhibitory activity of 56.37 ± 0.0059 % at 7 µg/ml; 59.16 ± 0.0137 % at 15 µg/ml; and 75.74 ± 0.0161 % at 28 µg/ml. This shows that the activity of quercetin-3-O-glucoside was lower than the active fraction (95.85 ± 0.0181%), but it was higher than the crude extract (64.23 ± 0.0562 %) at the highest tested concentration (28 µg/ml). On the other hand, kaempferol-3-O-glucoside was not tested due to its low availability after purification.

On the other hand, *Apium graveolens* exhibited unique and different ACE inhibition activity compared to other medicinal plants and its extracted compounds. *A. graveolens* had been fractionated into several compounds. The most significant compound that showed the highest inhibition activity among others, is a glucoside named junipediol-A-8-O-B-D glucoside with an IC_{50} value of 75.6 µg/ml. The other five compounds scarcely showed ACE inhibition activities. However, a synergistic study through Quantitative Structure-Activity Relationship (QSAR) illustrated the synergistic effect of these compounds with junipediol-A-8-O-B-D glucoside. The crude extract of *A. graveolens* exhibited 82.30 % of ACE inhibition activity at 5 mg/ml while junipediol-A-8-O-B-D glucoside exhibited only 64.00 % of ACE inhibition activity at 500 µM. On the contrary, when tested along with the other five compounds which include isofraxidin glucoside, reseoside, apigenin glucoside, luteolin glucoside, and icariside (all at concentration of 300 µM), the mixture of compounds have a higher percentage of ACE inhibition activity of 80.70 % at the same concentration.[18] This somehow indicates the role of synergism among the bioactive compounds in determining the net activity of the whole plant extract.

In summary, isolated bioactive compounds from *S. torvum* ((E)-2,3-dihydroxycyclopentyl-3-(3′,4′ dihydroxyphenyl) acrylate), and *M. oleifera* (quercetin-3-O-glucoside) have higher efficacy than the crude extract; while isolated bioactive compounds from *A. graveolens* (junepediol glucoside), *P. pellucida* (3',4', dihydroxy-3-5 dimethoxy flavone-7-O-β-rhamnose) have lower efficacy than the crude extracts in exhibiting the ACE inhibition activity. Among the plausible reason for the latter is perhaps due to the synergistic activity among few bioactive compounds in the crude extract.

CONCLUSION

In overall, this review clearly illustrates the potential of Southeast Asians' medicinal plants as ACE inhibitors in which several plants from Malaysia (*Chassalia curviflora, Citrus hystrix, Murraya koenigii, Senna garrettiana*), Indonesia (*Gnetum Gnemon, Momordica charantia, Nasturtium officinale, Peperomia pellucida, Pereskia saccharose*) and Thailand (*Mammea siamensis*) were found to exhibit strong ACE inhibitory activity *in vitro*. Bioactive compounds such as 3',4', dihydroxy-3-5 dimethoxy flavone-7-O-β-rhamnose and quercetin-3-O-glucoside showed the highest potency in exhibiting the ACE inhibition activity in this review. In conclusion, this review suggests for an in-depth investigation on the potent crude extracts for the potential development of complementary herbal medicines as well as on the potent ACE inhibitor compounds for further development as new ACE inhibitor candidates for hypertension therapy.

CONFLICTS OF INTEREST

The authors do not have any conflicts of interest regarding the content of the present work.

ACKNOWLEDGEMENT

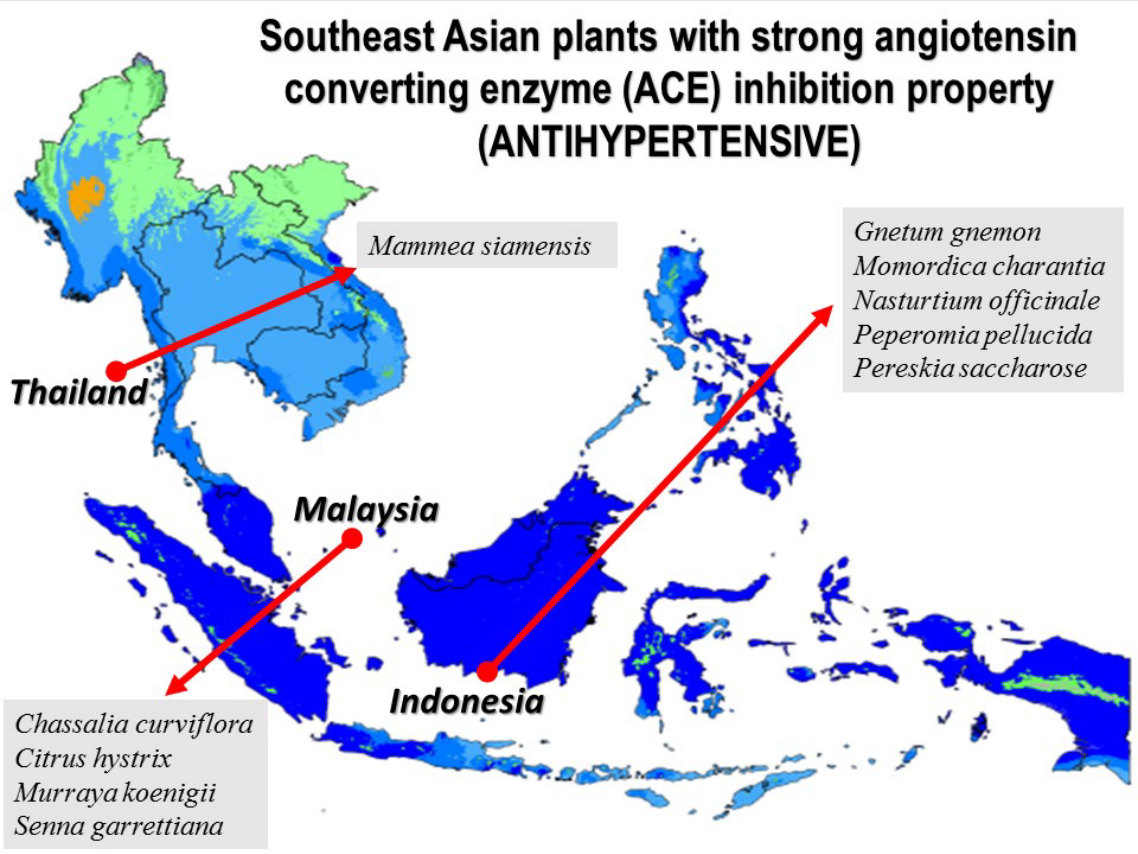
This research is funded by the Ministry of Higher Education, Malaysia with grant number FRGS/1/2018/SKK10/UIAM/02/1.

REFERENCES

1. Clark MA, Finkel RS, Rey JA, Whalen K. Lippincott's Illustrated Reviews: Pharmacology: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2012.
2. Zhou B, Bentham J, Di Cesare M, Bixby H, Danaei G, Cowan MJ, *et al*. Worldwide trends in blood pressure from 1975 to 2015: a pooled analysis of 1479 population-based measurement studies with 19· 1 million participants. Lancet 2017;389(1584):37-55.
3. Chow ZY, Jun SM, Ching SM, Tan CH, Lee KW, Devaraj NK, *et al*. Prevalence, awareness and control of hypertension in Malaysia 1980–2017: a systematic review and meta-analysis. BioRxiv 2019;625004:1-20.
4. Wong MKS. Subchapter 29A - Renin. In: Takei Y, Ando H, Tsutsui K, editors. Handbook of Hormones. San Diego: Academic Press; 2016.
5. Nurun Nabi AHM, Suzuki F, Inagami T. Chapter 11 - Renin. In: Rawlings ND, Salvesen G, editors. Handbook of Proteolytic Enzymes (Third Edition): Academic Press; 2013.
6. Chamata Y, Watson KA, Jauregi P. Whey-derived peptides interactions with ACE by molecular docking as a potential predictive tool of natural ACE inhibitors. Int J Mol Sci 2020;21(864):1-14.
7. Mans DR. Surinamese medicinal plants for treating hypertension with angiotensin-converting enzyme-inhibitory activity: a review of literature. Int J Med Res Health Sci 2018;7(11):26-48.
8. Arora PK, Chauhan A. ACE inhibitors: a comprehensive review. Int J Pharm Sci 2013;4(2):532-48.
9. Raia Jr JJ, Barone JA, Byerly WG, Lacy CR. Angiotensin-converting enzyme inhibitors: a comparative review. DICP, Ann Pharmacother 1990;24:506-25.
10. Dimou C, Antza C, Akrivos E, Doundoulakis I, Stabouli S, Haidich AB, *et al*. A systematic review and network meta-analysis of the comparative efficacy of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in hypertension. J Hum Hypertens 2019;33:188-201.
11. Pujiastuti DY, Ghoyatul Amin MN, Alamsjah MA, Hsu J-L. Marine organisms as potential sources of bioactive peptides that inhibit the activity of angiotensin I-converting enzyme: a review. Molecules 2019;24(14):1-16.
12. Braga FC, Serra CP, Viana Júnior NS, Oliveira AB, Côrtes SF, Lombardi JA. Angiotensin-converting enzyme inhibition by Brazilian plants. Fitoterapia 2007;78:353-58.
13. Barbosa-Filho JM, Martins VKM, Rabelo LA, Moura MD, Silva MS, Cunha EVL, *et al*. Natural products inhibitors of the angiotensin converting enzyme (ACE): a review between 1980 - 2000. Rer Bras Farmacogn 2006;16:421-46.
14. Ramesar S, Baijnath H, Govender T, Mackraj I. Angiotensin I-converting enzyme inhibitor activity of nutritive plants in KwaZulu-Natal. J Med Food 2008;11(2):331-36.
15. Rad SZK, Javadi B, Hayes AW, Karimi G. Potential angiotensin converting enzyme (ACE) inhibitors from Iranian traditional plants described by Avicenna's Canon of Medicine. Avicenna J Phytomed 2019;9(4):291-309.
16. Lemmens R, Soerianegara I, Wong WC. Plant Resources of South-East Asia. Indonesia: Backhuys Publishers; 1995.
17. Abdullah N, Ismail SM, Aminudin N, Shuib AS, Lau BF. Evaluation of selected culinary-medicinal mushrooms for antioxidant and ACE inhibitory activities. Evid Based Complementary Altern Med 2012;2012:1-12.
18. Simaratanamongkol A, Umehara K, Noguchi H, Panichayupakaranant P. Identification of a new angiotensin-converting enzyme (ACE) inhibitor from Thai edible plants. Food Chem 2014;165:92-97.
19. Muthia R, Suganda AG, Sukandar EY. Angiotensin-I converting enzyme (ACE) inhibitory activity of several Indonesian medicinal plants. Res J Pharm Biol Chem Sci 2017;8:192-99.
20. Singson DBB, Chichioco-Hernandez CL. Angiotensin-converting enzyme inhibitory action of selected plants. Sci Diliman 2017;29(2):97-101.
21. See GLL, Arce Jr FV, Deliman YC. ACE (angiotensin converting enzyme) inhibition activity of oven–dried and air–dried sambong *Blumea balsamifera* L.(dc.) Tea. Int J Pharmacogn Phytochem Res 2016;8(7):1132-36.
22. Loh SP, Hadira O. In vitro inhibitory potential of selected Malaysian plants against key enzymes involved in hyperglycemia and hypertension. Malays J Nutr 2011;17(1):77-86.
23. Rinayanti A, Radji M, Abdul Mi, Suyatna F. Screening angiotensin converting enzyme (ACE) inhibitor activity of antihypertensive medicinal plants from Indonesia. Int J Pharm Teach Pract 2013;4(1):527-32.
24. Khalid NM, Babji AS. Antioxidative and antihypertensive activities of selected Malaysian ulam (salad), vegetables and herbs. J Food Res 2018;7(3):27.
25. Kadir WNHW, Mhd Omar NA. Antihypertensive activity and phytochemicals analysis of *Chassalia curviflora* extracts collection of plant material. Int J Interdiscip Multidiscip Stud 2014;2(1):163-74.
26. Reyes RG, Kalaw SP, Gonzaga RJ, Dulay RM, Yoshimoto H, Kikukawa T, *et al*. Amino acid profile and anti-hypertensive activity of *Collybia reinakeana* P. Henn. Philipp Agric Sci 2010;93(3):263-68.

27. Tutor JT, Chichioco-Hernandez CL. Angioensin-converting enzyme inhibition of fractions from *Eleusine indica* leaf extracts. Pharmacogn J 2018;10(1):25-28.
28. Mun'im A, Munadhil MA, Puspitasari N, Yanuar A. Angiotensin converting enzyme inhibitory activity of Melinjo (*Gnetum gnemon* L.) seed extracts and molecular docking of its stilbene constituents. Asian J Pharm Clin Res 2017;10(3):243-48.
29. Hoe SZ, Kamaruddin MY, Lam SK. Inhibition of angiotensin-converting enzyme activity by a partially purified fraction of *Gynura procumbens* in spontaneously hypertensive rats. Med Princ Pract 2007;16:203-08.
30. Madaka F, Pathompak P, Sakunpak A, Monton C, Charoonratana T. Angiotensin I-converting enzyme inhibitor activity of some medicinal plants listed in traditional Thai medicine. Bull Health Sci Technol 2017;15(1):1-7.
31. Lestari P, Mahayasih PGMW. Inhibition activity of angiotensin converting enzyme (ACE) and determination of total phenolic and flavonoid compound from bitter melon leaves (*Momordica charantia* L.). Pharmacogn J 2017;9(2):252-56.
32. Acuram LK, Chichioco Hernandez CL. Anti-hypertensive effect of *Moringa oleifera* Lam. Cogent Biol 2019;5:1-10.
33. Lasboi E, Risyelly KB. Angiotensin I-converting enzyme inhibitory activity, total phenolic and flavonoid content of extract and fraction of jam fruit leaves (*Muntingia calabura* L.). Asian J Pharm Clin Res 2017;10:166-68.
34. Nhiem NX, Van Kiem P, Van Minh C, Tai BH, Cuong NX, Thu VK, *et al*. A new monoterpenoid glycoside from *Myrica esculenta* and the inhibition of angiotensin I-converting enzyme. Chem Pharm Bull 2010;58(10):1408-10.
35. Yaricsha CA, Rissyelly, Katrin. ACE inhibitory activity, total phenolic and flavonoid content of watercress (*Nasturtium officinale* R. Br.) extract. Pharmacogn J 2017;9(2):249-51.
36. Iswantini D, Rahminiwati M, Rohsela HN, Darusman LK. In vitro inhibition of water extract of kumis kucing and tempuyung towards angiotensin converting enzyme activity. Int J Adv Sci Eng Technol 2015;5:109-11.
37. Shafaei A, Khan MSS, Aisha AFA, Majid AMSA, Hamdan MR, Mordi MN, *et al*. Flavonoids-rich *Orthosiphon stamineus* extract as new candidate for angiotensin I-converting enzyme inhibition: a molecular docking study. Molecules 2016;21(11):1-16.
38. Mun'im A, Nurpriantia S, Setyaningsih R, Syahdi RR. Optimization of microwave-assisted extraction of active compounds, antioxidant activity and angiotensin converting enzyme (ACE) inhibitory activity from *Peperomia pellucida* (L.) Kunth. J Young Pharm 2017;9(1):S73-S78.
39. Kurniawan A, Saputri FC, Rissyelly, Ahmad I, Mun'im A. Isolation of angiotensin converting enzyme (ACE) inhibitory activity quercetin from *Peperomia pellucida*. Int J PharmTech Res 2016;9:115-21.
40. Lusiyanti SJ, Puspitasari N, Mahayasih PGMW. ACE inhibitory activity, total phenolic and flavonoid content of *Pereskia saccharose* Griseb. leaves extract. Pharmacogn J 2017;9(7):285-87.
41. Nhiem NX, Tai BH, Kiem PV, Minh CV, Cuong NX, Tung NH, *et al*. Inhibitory activity of *Plantago major* L. on angiotensin I-converting enzyme. Archives Pharm Res 2011;34(3):419-23.
42. Lau CC, Abdullah N, Aminudin N, Shuib AS. Effect of freeze-drying process on the property of angiotensin I-converting enzyme inhibitory peptides in grey oyster mushrooms. Dry Technol 2013;31(13-14):1693-700.
43. Desmiaty Y, Rahmat D, Rainoer AN. In vitro ACE, inhibitory activity and total flavonoids quantification of ethanolic extract of pletekan (*Ruellia tuberosa* L.) leaves. Indonesian Traditional Medicine for Human Welfare; 2014; Tawangmangu, Indonesia.
44. Nagappan H, Pee PP, Kee SHY, Ow JT, Yan SW, Chew LY, *et al*. Malaysian brown seaweeds *Sargassum siliquosum* and *Sargassum polycystum*: Low density lipoprotein (LDL) oxidation, angiotensin converting enzyme (ACE), α-amylase, and α-glucosidase inhibition activities. Food Res Int 2017;99:950-58.
45. Simaratanamongkol A, Umehara K, Niki H, Noguchi H, Panichayupakaranant P. Angiotensin-converting enzyme (ACE) inhibitory activity of *Solanum torvum* and isolation of a novel methyl salicylate glycoside. J Funct Foods 2014;11:557-62.
46. Suryani, Sukandar EY, Sutjiatmo AB, Vikasari SNAR. Angiotensin converting enzyme inhibitor activity of ethanol extract of *Sonchus arvensis* (Linn.) leaves. ACM International Conference Proceeding Series 2017;Part F1309:124-28.
47. Handa S. An overview of extraction techniques for medicinal and aromatic plants: United Nations Industrial Development Organization and the International Centre for Science and High Technology; 2008.
48. Seyfang BC, Klein A, Grützner T. Extraction centrifuges—intensified equipment facilitating modular and flexible plant concepts. ChemEngineering 2019;3(1):1-11.
49. Zhu Z, Jiang T, He J, Barba FJ, Cravotto G, Koubaa M. Ultrasound-assisted extraction, centrifugation and ultrafiltration: multistage process for polyphenol recovery from purple sweet potatoes. Molecules 2016;21(1584):1-13.
50. Nn A. A review on the extraction methods use in medicinal plants, principle, strength and limitation. Med Aromat Plants 2015;4(3):1-6.
51. Ćujić N, Šavikin K, Janković T, Pljevljakušić D, Zdunić G, Ibrić S. Optimization of polyphenols extraction from dried chokeberry using maceration as traditional technique. Food Chem 2016;194:135-42.
52. Jovanović A, Petrović P, Đorđević V, Zdunić G, Šavikin K, Bugarski B. Polyphenols extraction from plant sources. Lekovite Sirovine 2017;37:45-49.
53. Tiwari P, Kumar B, Kaur M, Kaur G, Kaur H. Phytochemical screening and extraction: a review. Int Pharm Sci 2011;1(1):98-106.
54. Siddesha JM, Angaswamy N, Vishwanath BS. Phytochemical screening and evaluation of in vitro angiotensin-converting enzyme inhibitory activity of *Artocarpus altilis* leaf. Nat Prod Res 2011;25(20):1931-40.
55. Williams LAD, Gossell Williams M, Sajabi A, Barton EN, Fleischhacker R. Angiotensin converting enzyme inhibiting and anti-dipsogenic activities of *Euphorbia hirta* extracts. Phytother Res 1997;11:401-02.
56. Ahmad I, Yanuar A, Mulia K, Mun'im A. Review of angiotensin-converting enzyme inhibitory assay: rapid method in drug discovery of herbal plants. Pharmacogn Rev 2017;11(21):1-7.
57. Jimsheena V, Gowda LR. Colorimetric, high-throughput assay for screening angiotensin I-converting enzyme inhibitors. Anal Chem 2009;81(22):9388-94.
58. Kumakura K, Kumakura H, Ogura M, Eguchi F. Pharmacological effects of *Ganoderma lucidum* collected from ume (Japanese apricot) trees. J Wood Sci 2008;54:502-08.
59. Kwon Y-II, Vattem DA, Shetty K. Evaluation of clonal herbs of *Lamiaceae* species for management of diabetes and hypertension. Asia Pac J Clin Nutr 2006;15(1):107-18.
60. Wanasundara PKJPD, Ross ARS, Amarowicz R, Ambrose SJ, Pegg RB, Shand PJ. Peptides with angiotensin I-converting enzyme (ACE) inhibitory activity from defibrinated, hydrolyzed bovine plasma. J Agric Food Chem 2002;50(24):6981-88.
61. Cushman DW, Cheung HS. Spectrophotometric assay and properties of the angiotensin-converting enzyme of rabbit lung. Biochem Pharmacol 1971;20:1637-48.
62. Ngo D-H, Ryu B, Kim S-K. Active peptides from skate (*Okamejei kenojei*) skin gelatin diminish angiotensin-I converting enzyme activity and intracellular free radical-mediated oxidation. Food Chem 2014;143:246-55.
63. Wu J, Aluko RE, Muir AD. Improved method for direct high-performance liquid chromatography assay of angiotensin-converting enzyme-catalyzed reactions. J Chromatogr A 2002;950(1-2):125-30.
64. Nakamura Y, Yamamoto N, Sakai K, Okubo A, Yamazaki S, Takano T. Purification and characterization of angiotensin I-converting enzyme inhibitors from sour milk. J Dairy Sci 1995;78:777-83.
65. Gao D, Chang T, Li H, Cao Y. Angiotensin I-converting enzyme inhibitor derived from cottonseed protein hydrolysate. Afr J Biotechnol 2010;9(53):8977-83.
66. Hurst PL, Lovell-Smith CJ. Optimized assay for serum angiotensin-converting enzyme activity. Clin Chem 1981;27(12):2048-52.
67. Meyer J, Bütikofer U, Walther B, Wechsler D, Sieber R. Hot topic: changes in angiotensin-converting enzyme inhibition and concentrations of the tripeptides Val-Pro-Pro and Ile-Pro-Pro during ripening of different Swiss cheese varieties. J Dairy Sci 2009;92:826-36.
68. Wijesinghe W, Ko S-C, Jeon Y-J. Effect of phlorotannins isolated from *Ecklonia cava* on angiotensin I-converting enzyme (ACE) inhibitory activity. Nutr Res Pract 2011;5(2):93-100.
69. Raghavan S, Kristinsson HG. ACE-inhibitory activity of tilapia protein hydrolysates. Food Chem 2009;117:582-88.
70. Shori AB, Baba AS, Chuah PF. The effects of fish collagen on the proteolysis of milk proteins, ACE inhibitory activity and sensory evaluation of plain-and *Allium sativum*-yogurt. J Taiwan Inst Chem Eng 2013;44(5):701-06.

GRAPHICAL ABSTRACT



ABOUT AUTHORS

T. A. Faiz T. Anuar: Tuan Faiz is currently an MSc student in Chemistry under Department of Chemistry, Kulliyyah of Science, International Islamic University Malaysia (IIUM).

Azlini Ismail: Azlini Ismail is an Assistant Professor at the Department of Fundamental Dental and Medical Sciences, Kulliyyah of Dentistry, International Islamic University Malaysia (IIUM). Her research interests include pharmacology, pharmacognosy, natural product, and traditional medicine.

Cite this article: Anuar TAFT, Ismail A. Southeast Asian Medicinal Plants with Angiotensin Converting Enzyme (ACE) Inhibition Properties. Pharmacogn J. 2020;12(6):1429-39.