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

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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.

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-aldoestosterone system (RAAS). RAAS involves several organs releasing enzymes including the kidney that releases renin which is also known as angiotensinogen. 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 pressure1,6 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 sulphydryl (-SH) containing...
Currently, few review papers have compiled the medicinal plants with ACE inhibition activity. Despite the therapeutic benefits of ACE inhibitors, sulphydryl (-SH) containing analogs lead to many side effects including skin rash and taste sense impairment because of its sulphydryl component presence; this has led to the development of non-sulphur captopril analogs such as enalapril and lisinopril. 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. 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. 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. Despite so, there are also some extracted bioactive compounds from various phytochemical groups in medicinal plants such as hydrolysable tannins, phenylpropanoids, proanthocyanidins, flavonoids, xanthones, fatty acids, terpenoids, alkaloids, oligosaccharides and peptide amino acids identified to have ACE inhibitory activity. Nonetheless, this review paper focuses on biopropecting 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; however, none of these papers focused on the medicinal plants from Southeast Asia region. Southeast Asia region is rich with undereveloped 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. 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 and Philippines. *Gynura procumbens* and *Orthosiphon stamineus* Benth were also studied in both Malaysia and Indonesia while *Apium graveolens* L was studied in Thailand and Indonesia.

**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. 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 and...
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. | Whole plants | Reflux | Ethanol 95% | Thailand | 37.91 ± 5.67 | 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 | 7.14 ± 1.71 | NA | 19 |
| Bactrya 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 | 143.00 | 1,367.00 | 19 |
| | Leaves | Maceration | Petroleum ether | Indonesia | NA | 402.00 | 23 |
| | Leaves | Maceration | Ethyl acetate | 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 | 22 |
| 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 | 24 |
| | Stipe | Maceration | Hot water | Philippines | 42.00 | NA | 24 |
| Cosmos caudatus | Whole herbs | Maceration | Hexane | Malaysia | 88.49 ± 0.85 | 5.00 | NA | 22 |
| | Whole herbs | Maceration | Dichloromethane | Malaysia | 51.00 | NA | 22 |
| Curcuma longa | Rhizome | Maceration | Water | Malaysia | 33.86 ± 0.96 | NA | 24 |
| Curcuma domestica Val | Rhizome | Maceration | Ethanol 95% | Indonesia | 24.15 ± 3.21 | NA | 19 |
| Cyclura barbara Miers. | Leaves | Maceration | Ethanol 95% | Indonesia | 35.57 ± 4.54 | NA | 19 |
| Elesine 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 gnemon l. | Seeds | Reflux | N-hexane | Indonesia | 79.29 | NA | 24 |
| | Seeds | Reflux | Dichloromethane | Indonesia | 89.92 | NA | 24 |
| | Seeds | Reflux | Ethylacetate | Indonesia | 92.10 | NA | 24 |
| | Seeds | Reflux | Methanol | Indonesia | 90.64 | NA | 24 |
| | Seeds | Reflux | Water | Indonesia | 89.90 | NA | 24 |
| Gynandropsis gynandra | Leaves | Maceration | Water | Malaysia | 35.55 ± 3.85 | NA | 24 |
| Species                     | Preparation                  | Extractants | Region    | IC50 Value          | Reference |
|-----------------------------|------------------------------|-------------|-----------|---------------------|-----------|
| *Gynura procumbens*         | Whole plant                  | Maceration  | Ethanol   | 800.00              | 24        |
|                             | Leaves                       | Maceration  | Petroleum ether | 432.00             | 23        |
|                             | Leaves                       | Maceration  | Ethyl acetate | 227.00              | 23        |
|                             | Leaves                       | Maceration  | Methanol   | 453.00              | 23        |
| *Heritium erinaceus*        | Fruiting bodies              | Infusion    | Distilled water | 580.00 ± 0.023     | 27        |
| *Hibiscus rosa-sinensis*     | Leaves                       | Maceration  | Petroleum ether | 431.00             | 23        |
|                             | Leaves                       | Maceration  | Ethyl acetate | 384.00              | 23        |
|                             | Leaves                       | Maceration  | Methanol   | 271.00              | 23        |
| *Mammea siamensis*          | Whole plants                 | Ultrasound-assisted extraction | Ethanol 95% | 97.50 ± 0.20         | 30        |
| *Manihot esculenta*         | Shoots                       | Maceration  | Hexane     | NA                  | 22        |
|                             | Maceration                   | Ditloromethane | Malaysia | 4.00                | NA        |
|                             | Maceration                   | Ethyl acetate | Malaysia | 27.00               | NA        |
| *Melia azedarach*           | Leaves                       | Maceration  | Petroleum ether | NA                 | 22        |
|                             | Leaves                       | Maceration  | Ethyl acetate | NA                 | 22        |
|                             | Leaves                       | Maceration  | Methanol   | NA                  | 22        |
| *Mesona palustris Bl.*      | Leaves                       | Maceration  | Ethanol 95% | 36.25 ± 5.71        | 19        |
| *Mespil ferrea*             | Whole plants                 | Ultrasound-assisted extraction | Ethanol 95% | 9.73 ± 0.09        | 38        |
| *Mimusops elengi*           | Whole plants                 | Ultrasound-assisted extraction | Ethanol 95% | 9.5 ± 0.30          | 38        |
| *Momordica charantia L.*    | Leaves                       | Maceration  | Ethanol    | NA                  | 7.52      |
|                             | Leaves                       | Maceration  | Ethyl acetate fraction | NA       | 4.29      |
| *Morinda citrifolia L.*     | Leaves                       | Maceration  | Ethanol 95% | 66.64 ± 2.32        | 22        |
| *Morus alba Linn.*          | Leaves                       | Maceration  | Ethanol 95% | 46.05 ± 3.07        | 19        |
|                             | Leaves                       | Maceration  | Ethanol    | NA                  | 22        |
|                             | Leaves                       | Maceration  | Ethyl acetate fraction | 22.00     | NA        |
|                             | Leaves                       | Maceration  | Methanol   | 28.00               | NA        |
|                             | Leaves                       | Maceration  | Methanol - ethyl acetate | 48.00    | NA        |
| *Muntingia calabura L.*     | Leaves                       | Maceration  | Ethanol    | NA                  | 1.25      |
|                             | Leaves                       | Maceration  | Ethyl acetate fraction | NA       | 0.63      |
| *Murraya koenigii*          | Leaves                       | Maceration  | Water      | 91.20 ± 4.15        | 24        |
| *Myrica esculenta*          | Leaves                       | Reflux      | Methanol   | 29.97               | NA        |
| *Nasturtium officinale R. Br.* | Herbs                      | Maceration  | Ethanol 95% | 51.94 + 2.92        | 19        |
|                             | Herbs                       | Maceration  | Ethanol 70% | 19.05               | NA        |
|                             | Herbs                       | Maceration  | Ethyl acetate fraction | 2.30     | NA        |
| *Nymphaea pubescens*        | Leaves                       | Maceration  | Methanol   | 32.00               | NA        |
|                             | Leaves                       | Maceration  | Methanol - hexane | 44.00    | NA        |
|                             | Leaves                       | Maceration  | Methanol – ethyl acetate | 11.00    | NA        |
| *Orthosiphon aristatus (Blume) Miq.* | Leaves                     | Maceration  | Water      | 69.20               | NA        |
| *Orthosiphon stamineus Benth.* | Leaves                     | Maceration  | Ethanol 95% | 55.41 ± 4.03        | 19        |
|                             | Leaves                       | Maceration  | Water      | NA                  | 358.80 ± 24.20 |
|                             | Leaves                       | Maceration  | Ethanol 100% | 45.80 ± 1.20       | 27        |
|                             | Leaves                       | Maceration  | Methanol 100% | 63.70 ± 1.10       | 27        |
|                             | Leaves                       | Maceration  | Ethanol 50% | 58.10 ± 2.00        | 27        |
|                             | Leaves                       | Maceration  | Methanol 50% | 78.20 ± 7.90       | 27        |
| *Oxalis corniculata*        | Leaves                       | Maceration  | Petroleum ether | NA                  | 439.00    |
|                             | Leaves                       | Maceration  | Ethyl acetate | NA                  | 325.00    |
|                             | Leaves                       | Maceration  | Methanol   | NA                  | 336.00    |
| *Peperomia pellucida (L.) Gaertn.* | Herbs                       | Microwave-assisted extraction | Ethanol-water | 54.73           | NA        |
|                             | Aerial Parts                 | Maceration  | Ethanol – ethyl acetate | 3.44     | NA        |
| *Pereskia saccharosa Griseb.* | Leaves                     | Maceration  | Ethanol    | NA                  | 3.45      |
|                             | Leaves                       | Maceration  | Ethyl acetate | 1.71 x 10^-3     | 46        |
| *Persea americana Mill.*    | Leaves                       | Maceration  | Ethanol 95% | 29.49 ± 6.24        | 39        |
| *Persea americana*          | Seeds                        | Maceration  | Petroleum ether | NA                  | 1,043.00  |
|                             | Seeds                        | Maceration  | Ethyl acetate | NA                  | 476.00    |
|                             | Seeds                        | Maceration  | Methanol   | NA                  | 500.00    |
Malaysian seaweeds.\(^4\) 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.\(^2\) 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 on the solvent 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.\(^4\)

Ultrasound-assisted extraction was used in extracting some medicinal plants such as *Mammea siamensis*, *Mesue ferrea*, *Mimusops elengi* and *Senna garrettiana*.\(^5\) 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.\(^5\) 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 breaks 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.20 From the reported studies, there are distinguished methodological preferences in conducting maceration especially the temperature, period, and also solidsolvent ratio. For temperature during maceration, most of these researches used room temperature 24,27,29 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 20 and some studies used longer maceration period, such as 24 hours 24, 48 hours 27,29, and the longest period of maceration was 72 hours.36,27,48 As for solid-solvent ratio, several studies mentioned that the ratio of 1:10 46, 1:8 46 and also 1:52 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.13 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.5,15,16,51 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.28

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 IC50 values of 45.8, 63.7, 58.1, and 78.2 µg/ml, respectively.53 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 IC50 for extraction via methanol than via petroleum ether.24 Meanwhile, the seeds of Gnetum gnemon L. at 100 µg/ml exhibited increased 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.24,52 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 23 and Murraya koenigii.22 Ethanol 100 % and 95 % were used to extract Monordica charantia 21, Muntingia calabura 21, Pereskia sacharose 20, Mammee siamensis 20, and Senna garrettiana.30 Methanol was also used to extract C. curviflora 25 and G. gnemon.20 Apart from the polar solvent, plants such as G. gnemon 20 and P. sacharose 46 which were being extracted using ethyl acetate, a semi-polar solvent, also have highly significant ACE inhibition activity. However, in some studies, the IC50 values of plants extracted using methanol or ethanol were smaller than the IC50 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; and also the usage of different methods of HA measurement including of microplate reader or High-Performance Liquid Chromatography (HPLC).54,59

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-hydroxybutylglycyl-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 (HHB). 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. Meanwhile the Holmquist method utilizes tripeptide furenacryloyl (FA-PPG) substrate.38 ACE reacts upon FA-PPG to form dipeptide (glycylglycine) and furanacryloyl-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 hystrix (at 500 µg/ml), Gnetum Gmono l. (at 100 µg/ml), Mammee siamensis (at 1000 µg/ml), Murraya Koennigia (at 500 µg/ml) and Senna garrettiana (at 1000 µg/ml).
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 | 18 |  |
| 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-hydroxybutylglycyl-glycy-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 IC₅₀ 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 |
|                       | Lateolin-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       | Corchoinoides C (65,9R)-Roseside      | Leaves       | ACE inhibitory activity of 29.97 % | 34 |
|                       | Myricanol                             | Leaves       | ACE inhibitory activity of 25.63 % | 34 |
|                       | 5-Ob-D glucopyranosyl myricanol       | Leaves       | Weak ACE inhibitory activity. | 34 |
|                       | Myricetin                             | Leaves       | Weak ACE inhibitory activity. | 34 |
|                       | 3',4'-Dihydroxy-3-5 dimethoxy flavone-7-O-b-rhamnose | Aerial parts | High ACE inhibitory activity with IC₅₀ value of 7.72 μg/ml. | 38 |
**Plantago major L.**

| Component                          | Form   | ACE Inhibition Activity |
|------------------------------------|--------|-------------------------|
| 10-Hydroxy-majorside               | Leaves | High ACE inhibitory activity of 28.06% at concentration of 100 µM. |
| γ'-β-D-Glucopyranoside             | Leaves | Weak ACE inhibitory activity. |
| 6-Hydroxyapigenin 7-O-beta-D-glucoside | Leaves | Weak ACE inhibitory activity. |

**Solanum torvum**

- (E)-2,3-Dihydroxycyclopentyl-3-(3',4' dihydroxyphenyl) acrylate
- Laricresinol-4,4'-O-β-D-diglucoside
- Methyl salicylate glycoside

| Component                          | Form    | ACE Inhibition Activity |
|------------------------------------|---------|-------------------------|
| Fruits                             |         | Scarcely showed any ACE inhibitory activity. |

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 %), Morea citrifolia L. (66.64 %), Nasturtium officinale R. Br. (51.94 %), Orthosiphon aristatus (Blume) Miq. (69.20 %), Orthosiphon staminus 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 %) Scyzygium polyanthum (Wight) Wap (53.37 – 75.00 %) and also Zea mays (50.44 %).

Several plants have more than one value of percentage inhibition activity as different studies were reported on the same plant, for example for C. Caudatus with the ACE inhibition values of 51.00 %and also 88.49 %; S. polyanthum (Wight) Wap with the ACE inhibition values of 53.37 %and 75.00 %; and also A. bilimbi L. with the ACE inhibition values of 65.00 %; 70.42 % and 79.18 %. 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 IC50, a usual measure of the potency of any drugs or any potential drug candidates. For instance, the lower the IC50, the more potent the drug. Twenty-eight medicinal plants in this review paper have reported the plant's IC50 values. Among these plants, six plants were identified as highly potent, indicated by a very low IC50 which was lower than 10 µg/ml. These plants are Chassalia curviflora, Monordica charantia, Muntingia calabura, Nasturtium officinale R. Br., Persika scacharos Griseb and Peperomia pellucida (L.) Kunth.

C. curviflora leaves and flower exhibited ACE inhibition activity with IC50 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. For M. charantia L., both its ethanol crude extract and ethyl acetate fraction exhibited low IC50 values of 7.54 µg/ml and 4.29 µg/ml respectively. The same goes for M. calabura L., both its ethanol crude extract and ethyl acetate fraction also showed low IC50 values of 1.25 µg/ml and 0.63 µg/ml respectively. In addition to that, N. Officinale R. Br. ethanol crude extract exhibited an IC50 value of 19.05 µg/ml, but its ethyl acetate fraction showed a much lower IC50 value of 2.30 µg/ml. These studies indicated that the ethyl acetate fraction of these plants exhibited higher ACE inhibition than the crude ethanolic extract. As for P. scacharos Griseb, both its ethanol and ethyl acetate crude extracts illustrated high potency with IC50 values of 3.448 µg/ml and 1.714 x 10-3 µg/ml respectively. Lastly, the P. pellucida (L.) Kunth ethyl acetate fraction has an IC50 value of 3.44 µg/ml.

There are also other plants with significant ACE inhibition activity with reported IC50 values from 10 µg/ml to 100 µg/ml. These include G. lucidum, N. officinale, P. cystidiosus, P. eryngii, P. flabellate, P. florida, P. sajor-caju, P. tuberosa, S. polycystum, and S. arvens. With IC50 values of 50.00, 19.05, 54.00, 67.00, 58.00, 50.00, 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., Moringa oleifera Lam, Myrrica esculenta, Peperomia pellucida (L.) Kunth, Plantago major L., and Solanum torvum. The crude extract of S. torvum studied by Simaratananmongol et al. showed moderate inhibition against ACE enzyme at the concentration of 5 mg/ml. While the IC50 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 IC50 than the crude extract with an IC50 value of 778 µg/ml, indicative for a higher potency than the crude extract.

As for Plantago major L., Nhiem et al. tested eight isolated compounds and they found that only one compound, 10-hydroxy-majorside 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 IC50 value of 3.44 µg/ml, meanwhile, its flavonoid compound, 3',4'-dihydroxy-3-5 dimethoxy flavone-7-O-β-rhamnose with an IC50 value of 7.72 µg/ml was less potent than the crude extract. For Myrrica esculenta, several metabolites have been isolated but only corchoinoside 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.

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.
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 ± 0.0062 %) 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 IC₅₀ 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 isoarxinidin glucoside, resesose, 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. 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-dihydroxycyclopentol-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* (junipediol glucoside), *P. pellucida* (3′, 4′ 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 *Senna garrettiana*) 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.

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**GRAPHICAL ABSTRACT**

Southeast Asian plants with strong angiotensin converting enzyme (ACE) inhibition property (ANTIHYPERTENSIVE)

- **Mammea siamensis**
- **Gnetum gnemon**
- **Momordica charantia**
- **Nasturtium officinale**
- **Peperomia pellucida**
- **Pereskia saccharosa**
- **Chassalia curviflora**
- **Citrus hystrix**
- **Murraya koenigii**
- **Senna garrettiana**

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