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1 The potential of various seeds as angiotensin-I converting enzyme inhibitory peptides derived from protein hydrolysate: a short review

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Abstract. 4
Angiotensin-I converting enzyme (ACE) plays an imperative role in the blood pressure system. It generates intense vasoconstriction by converting angiotensin-I to angiotensin-II. Counter regulation of ACE may reduce blood pressure. One of the most frequently used medications for treating hypertension cases to inhibit ACE activity is a commercial synthetic drug. However, long-term consumption of those drugs could lead to suffering dangerous and unpredictable side effects. There have been many studies recently concerning the bioactive peptides as ACE inhibitors derived from various seeds. It has been reported that non-thermal extraction methods were used to obtain the protein from inside the cell. However, there was a lack of information focusing on ACE inhibitory peptides from plant biomass. Therefore, this review aimed to summarise and gather the point of view of the plant-derived ACE inhibitory peptides from raw material sources, processing, and peptide sequences studies. This paper contributed to explaining a comprehensive review of ACE inhibitory peptides from edible materials and proposes a fascinating discussion due to the sources being discovered derived from edible protein and safer grade. Various seeds in Indonesia may have future potential for ACE inhibitory peptides as natural therapeutic agents.

1. Introduction

Cardiovascular disease (CVD) has become the number one cause of death globally, representing 95% mortality [1]. CVD has been related to many conditions that cause abnormal cardiovascular systems, such as aorta disease, congenital heart disease, coronary artery disease, heart attack, rheumatic heart disease, and stroke [2]. Among CVD risk factors, high blood pressure (HBP) is the principal and critical case for CVD [3]. There are many multiple medications in patients with hypertension, such as angiotensin receptor blockers (ARBs), thiazide diuretics, calcium channel blockers, angiotensin-I



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converting enzyme (ACE) inhibitors and beta-blockers [4]. However, ACE inhibitors (ACEIs) have been recommended as the most prescribed medication to treat HBP [5].

The classical renin-angiotensin-aldosterone system (RAAS) regulates a superlative role in controlling blood pressure due to ACE's activity produces angiotensin II as a vasoconstrictor, which is generated from the angiotensin I [6]. In the meantime, ACE also degrades bradykinin as a vasodilator. Those two actions strengthen to elevate HBP condition. Several synthetic commercial ACEI drugs have strong effectively proven to alleviate hypertension, such as captopril, enalapril, lisinopril, fosinopril, and benazepril. However, those drugs are believed to have some side effects, such as cough, allergic skin rashes, fatigue, loss of taste, and sleep apnea [7]. Therefore, discovering the ACEIs from natural sources as therapeutic agents is a fascinating study.

Recently, several studies have been reported that plant-derived peptide could be used as alternative ACEIs, such as *Camellia oleifera* Abel seed [8], cotton seed [9], date seed [10], *Ginkgo biloba* seed [11], hemp seed [12], longan seed [13] and peach seed [14]. That biomass is classified as plant-seed. The activity of bioactive peptides from natural sources as ACEIs may be less effective than synthetic drugs. Still, ACEI peptides are regarded as safer since their degraded products in the human digestive system are amino acids. Not only ACEI peptides are researched from plants, but also their sources have been explored from animals. Plant-derived peptides as alternative therapeutic agents are considered the potential ones because they are renewable and environmentally sustainable biomass. Remarkably, the utilisation of seeds is limited as crop cultivation, and vegetarians may prefer plant sources.

ACEI peptides are allowed to leave seeds for the chosen ones by specific steps. The simple steps to obtain the bioactive peptides are divided into four stages: extraction, proteolysis, fractionation, and characterisation. Physical, chemical, and biological extraction methods have been tried to remove the protein or peptides from the inside cell. Non-thermal processing has been developed extensively in recent studies due to its technology keeps the natural chemical structure. Continually, proteolysis releases the peptides from whole proteins with two different conditions, specifically hydrolysis enzymatic and fermentation conditions.

Additionally, screening is a method to select the highest ones of a bioactive peptide as ACEI. The last way to identify ACEI peptides' properties is characterisation with many analyses, such as *in vitro*, *in vivo*, and *in silico*. As far as we know, review studies on various seeds have not been reported previously. This study will give particular attention to seeds that are categorised as vegetable, flower, and fruit. Therefore, this paper aims to review focusing the current novel on seed-derived ACE-inhibitory peptides covering their raw material sources, processing, and peptide sequences studies.

2. Extraction and Miscellaneous Techniques in ACEI Peptides Release

Natural provided bioactive peptides have been found in fermented food products, and the human gastrointestinal tract due to their established sequences are originated from short protein fragments that have positive biological activity in the human metabolism system [15]. The functionality of bioactive peptides may differ based on their peptide sequences. Before obtaining bioactive peptides, several developed methods to get the whole proteins as materials are the most critical thing. Those whole proteins would be hydrolysed into bioactive peptides, which functions as ACE inhibitory peptides. Size reduction of seeds is usually introduced to increase the plant seed's surface area. Size reduction enhances the retraction mass transfer from inside of the plant matrix.

Physical disruption is a cheap and simple method to extract the whole proteins from the inside cells. The principle is by rupturing the plant cell wall and its constituents would come out. The thermal extraction process was not recommended since it has high-cost efficiency. Therefore, the non-thermal process is the emerging technology suggested for the extraction process. Several non-thermal processing technologies (e.g., ultrasound, cold plasma, pulsed electric field, and high-pressure treatments) have an impact on increasing yield, protein hydrophobicity, protein structures, and functionalities [16]. High-pressure treatment in the range of 100–300 MPa can increase proteolytic enzyme activity [17]. The extraction using pulsed electric field (PEF) is recommended at low electric field strength (2.5–10 kV/cm)

[18, 19]. While treatment process at high electric field strength (>30 kV/cm) led to a decrease in solubility, surface free sulfhydryl, and hydrophobicity of protein isolates [20].

It has been reported that only two methods were used to gain the whole protein from various seeds to utilise as ACE inhibitory peptides, particularly ultrasonication and chemical solvent extraction [21, 9]. Chemical solvent extraction aims to remove full-fat seeds which is called defatted seeds [10]. Occasionally, this liquid extraction consists of more than one solvent used in several stages of extraction that means in certain stages are utilised as protein dissolution. In addition, protein precipitation was used due to its necessity for protein purity. Further research is possible to carry out the seed extraction process using several non-thermal technologies that have been previously mentioned as ACE inhibitory peptides.

There are some processing methods to obtain the selected candidate as ACE inhibitory peptide from seeds, as shown in Figure 1. These peptides are released by proteolytic enzyme. It has been reported that proven some proteases produced potent peptides with high activity as ACE inhibitory peptides, such as alkaline protease, papain, alcalase, thermolysin, pepsin, pancreatin, trypsin, and α -chymotrypsin, as shown in Table 1. Hydrolysates are a complex mixture of free amino acids and peptides with diverse chain length peptides and sequences produced by certain hydrolysis conditions. In basic hydrolysis, the protease activity is determined by its optimum conditions, such as time, temperature, pH, and enzyme to substrate (E/S) ratio. As reported previously, optimisation treatment is necessary for controlled proteolysis production of the single targeted peptide as ACE inhibitory peptide [22].

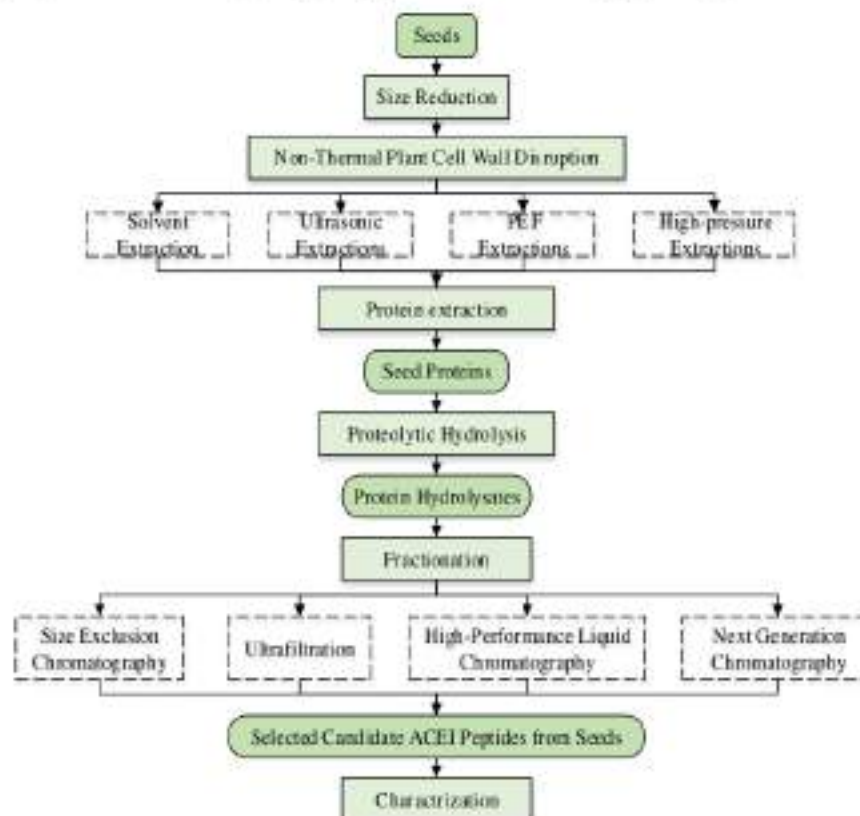


Figure 1. Outline of production scheme in releasing ACE inhibitory peptides from various seeds.

The proteolytic enzyme plays a notable role in determining the ACE inhibition activity due to the specificity of protease accommodating conformation of peptide sequences. The peptides with a small molecular weight and categorically residue take the position of an inhibitor entering the enzyme's active site. A combined enzyme has been used to obtain the shorter peptide fragments, which increases the ability of ACE inhibitory peptides [10]. Furthermore, gastrointestinal protease was also used to generate tolerable fragments through the gastrointestinal tract due to some sequences that could be digested by the gastrointestinal digestion enzyme [23]. Therefore, it is crucial to select the proper enzyme for significant endeavour strides to develop an influential ACE inhibitory peptide.

Fractionation of protein hydrolysate is one stage to separate the mixture of peptides from screening the highest single peptide followed by *in vitro* tested ACE inhibitory activity on each fraction. Variegated fractionation methods to obtain ACE inhibitory peptides from seeds have been summarised as follows: (1) size exclusion chromatography (SEC); (2) ultrafiltration (UF); (3) high-performance liquid chromatography (HPLC); and (4) next-generation chromatography (NGC), as shown in Figure 1. Ultrafiltration is a system for separating suspended solids, which utilises hollow membrane fibres with various pore size and molecular weight cut-off (MWCO). This method is used as the initial technique before fractionating in chromatography technique and commonly method combined with the other fractionation techniques in most cases. Furthermore, characterisation is the final step to describe the peptide properties as prospect ACE inhibitor assessed by *in vitro*, *in vivo*, and *in silico*.

Table 1. Raw materials, proteolytic, fractionation methods, peptide sequences and IC₅₀ values of angiotensin-I converting enzyme inhibitory peptides derived from seeds.

| Raw Material | Proteolytic | Fractionation Method | Peptide Sequence | IC ₅₀ Value | Ref. |
|-----------------------------------|--|--|--------------------------|------------------------------------|------|
| <i>Camelia oleifera</i> Abel seed | Alkaline protease | UF <1kDa, SEC with Sephadex G-15, RP-HPLC | - | 0.678 mg/mL | [8] |
| Cottonseed | Papain | UF 5-10 kDa, SEC with Sephadex G-25, RP-HPLC | FPAIGMK | 46.7 μg/mL | [9] |
| Date seed | Alcalase + thermolysin | - | - | 0.53 mg/mL | [10] |
| <i>Gingko biloba</i> seed | Alcalase | UF <1 kDa, SEC with Sephadex G-15, semi-preparative HPLC | RVFDGAV | 1,006 mM | [11] |
| Hemp seed | Papain | SEC with Superdex Peptide-10/300 GL column | - | 0.1 mg/mL | [12] |
| Longan seed | Pepsin and pancreatin | UF (>10, 5-10, 3-5, <3 kDa), RP-HPLC | ETSGMKPTEL ISSMGILVCL | 2.15 ± 0.016 μM 3.88 ± 0.004 μM | [13] |
| Peach seed | Thermolysin | UF <3 kDa, RP-HPLC | IYPSH | 24 ± 3 μg/mL | [14] |
| Prickly ash seed | Papain | UF (>5, <5 kDa), SEC with Sephadex G-25 | - | 0.021 ± 0.007 mg/mL | [33] |
| Sesame seed | Simulated gastrointestinal digestion <i>in vitro</i> (pepsin, trypsin, α-chymotrypsin) | UF (>100, 50-100, 30-50, 10-30, 5-10, 3-5, <3 kDa), NGC Chromatography | GHTVAR | 3.60 ± 0.10 μM | [23] |
| Bitter melon seed | Thermolysin | UF <3 kDa, RP-HPLC | VSGAGRY | 8.64 ± 0.60 μM | [21] |

3. ACEI Peptides Properties from Seeds and Its Evaluation Activity

3.1. *In vitro*

Analysis of ACEI activity has been found with the various substrate, chemical, and analytical techniques, such as spectrophotometric, radiochemical, HPLC, capillary electrophoresis, mass spectrometric methods, and fluorometric [24, 25, 26, 27, 28, 29]. Among them, invariably used method was performed using spectrophotometric techniques [24]. The potential of the peptide was evaluated using IC_{50} value due to its value represented the concentration of a substance as a therapeutic agent that is obligated for 50% inhibition *in vitro*. Although there is no correlation between competitive inhibitor with a strong IC_{50} value of ACE inhibitory activity, a kinetic study of inhibitor-enzyme reaction must investigate the inhibition type of enzyme.

As seen in Table 1, provided fractionations used in each study means hierarchy steps to obtain the best ACEI peptide candidate. The first and second highest IC_{50} values of ACEI peptides were $2.15 \pm 0.016 \mu\text{M}$ and $3.60 \pm 0.10 \mu\text{M}$ from longan seed and sesame seed, respectively [13, 23]. Their hierarchical fractionation was five and eight steps, which usually started by UF (from higher to smaller size of MWCO) and ended by chromatography were long enough steps to explore small fragments ETSGMKPTL and GHITVAR. Some IC_{50} values with their identified sequences were analysed using synthetic peptides with the confirmed purity greater than 95%. The high purity peptide with the synthetic one can quickly characterise the peptide profile as ACEI, such as bioavailability, kinetic study, and animal study.

It has been specified that shorter peptide fragments and tripeptide exhibit strong ACE inhibitory peptide with the amino acid sequences, N-terminal hydrophobic, a positively charged at the middle, and C-terminal an aromatic residue [30]. However, previous studies have not yet reported that tripeptide was found from various seeds. It is reasonable to use thermolysin to exert ACE inhibitory peptides with high inhibition activity. Thermolysin preferentially cleaves at N-terminal containing hydrophobic residues that were studied with the significance of IC_{50} values from ISSMGILVCL and VSGAGRY were $3.88 \pm 0.004 \mu\text{M}$ and $8.64 \pm 0.60 \mu\text{M}$, respectively [13, 16]. Simulated gastrointestinal digestion was also used to evaluate the bioavailability in the human gastrointestinal tract due to the peptide is easily digested by gastrointestinal protease.

3.2. *In vivo*

In vivo assay is a method to characterise peptides' bioactivity in living organisms. The method is investigated using spontaneously hypertensive rats (SHRs). The measurement of antihypertensive effects is evaluated after intragastric intubation with a periodic time from systolic blood pressure using the tail-cuff method. *In vitro* testing of peptides is performed using many comparable concentrations, diverse protein hydrolysates, and synthetic drugs. In several cases, the fragments after oral administration exhibited a smaller number of hypotensive effects than commercial medications due to the complex metabolism in animals. For example, protein hydrolysate of hemp seed using alcalase was the best hypotensive effect than all protein hydrolysate using various proteolytic enzymes in 8 hours after oral administration. However, alcalase-hydrolyzed peptides had no long-term hypotensive effect after 24 administered compared to the other hydrolysates [12]. This phenomenon is probably because of the degradation of peptide fragments by gastrointestinal enzymes. On the other hand, VSGAGRY with the IC_{50} value of $8.64 \pm 0.60 \mu\text{M}$ showed a dramatically higher hypotensive effect than captopril. Although there is no direct correlation between *in vitro* ACE inhibitory assay and *in vivo* antihypertensive activity, it is considered to know the peptide profile in animal studies because these therapeutic agents would be consumed orally.

3.3. *In silico*

In silico analysis, drug discovery of interaction mechanism between peptide is widely applied as an inhibitor towards ACE as an enzyme. This molecular docking approach is also used as an evidence illustration from *in vitro* kinetic study. The selected peptide of RVFDGAV from *Ginkgo biloba* seed was demonstrated as a competitive inhibitor based on the Lineweaver-BZurk plot, which is matching

with computational modelling with hydrogen bonds formed in some drug-like residues, specifically Ala354O, Tyr523OH, His353NE2, Glu162OE2 [11]. Also, ETSGMKPTL is regarded as a non-competitive inhibitor from kinetic study and corresponds with the molecular docking prediction, which is no similarity interaction of the ACE-lisinopril complex as a competitive inhibitor standard interaction [13]. Several methods with specific docking parameters are arranged to predict in facilitating the best scoring docked pose. Affinity score and spacing of ligand-macromolecular interaction are suitable assessments to classify the potent peptide within regularity binding conformation compared to commercial drugs [31, 32].

Previously studies on seeds-derived peptides by bioinformatic modelling were demonstrated using seven software, such as CHARMM, GoldScore, ChemScore, ChemPLP, ASP, Molegro Virtual Docker and Surflex-Dock [11, 13, 21, 18]. The lowest docking score is corresponding to the lowest binding energy that indicates the predictable docking result. In-depth investigations about an enzyme's binding mechanism with peptide are the substantial assessment to look at the similar binding site with the commercial drugs. Several studies focused on the binding mechanism between peptides and the essential residue of Zn (II) binding motif HEXXH (His-Glu-X-X-His). Moreover, interaction established hydrogen bond formation of peptide-ACE is monitored in angstrom (Å) as a distance unit to understand the strengths and complexity of ligand-protein conformation. Those observed residues of ACE were Glu162OE2, His353NE2, Ala354O, Glu384OE2, Lys511NZ, His513NE2, Tyr520OH, and Tyr523OH.

4. Conclusions

ACE inhibitory peptides derived from various seeds are promising alternatives to solve the hypertension cases and are stated as therapeutic representatives as natural products. Although some studies have shown that peptides can be degraded through the digestive system, the degraded smaller peptides also show its potential as an ACE inhibitor. Growing consumer trend preferences as vegetarianism in recent years that means to be an important decision to explore ACE inhibitory peptides from plant sources. Nutrition plays a pivotal role in preventing many chronic diseases. Moreover, fermented food consumption is a straightforward action from this effort to preventive healthcare for hypertension due to its source of bioactive peptides and classified as a functional food.

References

- [1] Jagannathan R, Patel S A, Ali M K, Narayan K M V 2019 Global updates on cardiovascular disease mortality trends and attribution of traditional risk factors *Curr. Diab. Rep.* **19** 44
- [2] Perk J, De Backer G, Gohlke H, Graham I, Reiner Z, Verschuren W M, Albus C, Benlian P, Goysen G, Cifkova R, Deaton C, Ebrahim S, Fisher M, Germano G, Hobbs R, Hoes A, Karadeniz S, Mezzani A, Prescott E, Ryden L, Scherer M, Syv anne M, Op Reimer W J M S, Vrints C, Wood D, Zamorano J L, Zannad F 2012 European guidelines on cardiovascular disease prevention in clinical practice: the fifth joint task force of the european society of cardiology and other societies on cardiovascular disease prevention in clinical practice *Eur. Heart J.* **33** 13 1635-1701
- [3] Fuchs F D, Whelton P K 2019 High blood pressure and cardiovascular disease *Hypertension* **75** 2 285-292
- [4] Richards T R, Tobe S W 2014 Combining other antihypertensive drugs with β -blockers in hypertension: a focus on safety and tolerability *Can. J. Cardiol.* **30** 5 S42-S46
- [5] Messerli F H, Bangalore S, Bavishi C, Rimoldi S F 2018 Angiotensin-converting enzyme inhibitors in hypertension: to use or not to use? *J. Am. Coll. Cardiol.* **71** 13 1474-1482
- [6] Jiang F, Yang J, Zhang Y, Dong M, Wang S, Zhang Q, Liu F F, Zhang K, Zhang C 2014 Angiotensin-converting enzyme 2 and angiotensin 1-7: novel therapeutic targets *Nat. Rev. Cardiol.* **11** 413-426
- [7] Yilmaz I 2019 Angiotensin-converting enzyme inhibitors induce cough *Turk Thorac J.* **20** 1 36-42
- [8] Yao G L, He W, Wu Y G, Chen J, Hu X W, Yu J 2019 Purification of angiotensin-I-converting

- enzyme inhibitory peptides derived from *Camellia oleifera* seed meal hydrolysate. *J. Food Quality* **1-9**
- [9] Gao D, Zhang F, Ma Z, Chen S, Ding G, Tian X, Feng R 2019 Isolation and identification of angiotensin-I converting enzyme (ACE) inhibitory peptides derived from cottonseed protein: optimisation of hydrolysis conditions *Int. J. Food Prop.* **22** 1 1296-1309
- [10] Ambigaipalan P, Al-khalifa A S, Shahidi F 2015 Antioxidant and angiotensin I converting enzyme (ACE) inhibitory activities of date seed protein hydrolysates prepared using alcalase, flavourzyme and thermolysin *J. Funct. Foods* **18** 1125-1137
- [11] Ma F F, Wang H, Wei C K, Thakur K, Wei Z J, Jiang L 2019 Three novel ACE inhibitory peptides isolated from *Ginkgo biloba* seeds: purification, inhibitory kinetic and mechanism *Front. Pharmacol.* **9** 1579
- [12] Malomo S A, Onuh J O, Girgih A T, Aluko R E 2015 Structural and antihypertensive properties of enzymatic hemp seed protein hydrolysate *Nutrients* **7** 7616-7632
- [13] Nuchrapha A, Paisansak S, Sangtanoo P, Srimongkol P, Saisavoey T, Reamrong O, Choowongkamon K, Karachanata A 2020 Two novel ACE inhibitory peptides isolated from longan seeds: purification, inhibitory kinetics and mechanism *RSC Adv.* **10** 12711-12720
- [14] Villanueva R V, Orellana J M, Marina M L, Garcia M C 2019 Isolation and characterisation of angiotensin converting enzyme inhibitory peptides from peach seed hydrolysate: in vivo assessment of antihypertensive activity *J. Agric. Food Chem.* **67** 37 10313-10320
- [15] Daliri E B W, Oh D H, Lee B H 2017 Bioactive Peptides *Foods* **6** 532
- [16] Esteghlal S, Gahruei H, Niakousari M, Barba F J, Bekhit A E, Mallikarjunan K, Roohinejad S 2019 Review: Bridging the knowledge gap for the impact of non-thermal processing on proteins and amino acids *Foods* **8** 7 262
- [17] Peñas E, Préstamo G, Polo F, Gomez R 2006 Enzymatic proteolysis, under high pressure of soybean whey: Analysis of peptides and the allergen Gly m 1 in the hydrolysates *Food Chem.* **99** 569-573
- [18] Putranto A W, Argo B D, Wijana S 2014 Green pulsed electric field-assisted extraction method of total carotenoid carrot pulp using olive oil as solvent *Indonesian Green Technology Journal* **3** 1 1-9
- [19] Putranto A W, Dewi S R, Puspitasari Y, Nuriah F A 2018 Optimization of free radical scavenging capacity and pH of *Hylocereus polyrhizus* peel by Response Surface Methodology. *IOP Conference Series: Earth and Environmental Science* 2018 **131** 1 012051
- [20] Li Y, Chen Z, Mo H 2007 Effects of pulsed electric fields on physicochemical properties of soybean protein isolates *LWT Food Sci. Technol.* **40** 7 1167-1175
- [21] Priyanto A D, Doerksen R J, Chang C I, Sung W C, Widjanarko S B, Kusnadi J, Lin Y C, Wang T C, Hsu J L 2015 Screening, discovery, and characterisation of angiotensin-I converting enzyme inhibitory peptides derived from proteolytic hydrolysate of bitter melon seed proteins *J. Proteomics* **128** 424-435
- [22] Priyanto A D, Doerksen R J, Chang C I, Sung W C, Widjanarko S B, Kusnadi J, Lin Y C, Wang T C, Hsu J L 2015 Data in support of optimised production of angiotensin-I converting enzyme inhibitory peptides derived from proteolytic hydrolysate of bitter melon seed proteins *Data in Brief* **5** 403-407
- [23] Wang R, Lu X, Sun Q, Gao J, Ma L, Huang J 2019 Novel ACE inhibitory peptides derived from simulated gastrointestinal digestion in vitro of sesame (*Sesame indicum* L.) protein and molecular docking study *Int. J. Mol. Sci.* **21** 3 1059
- [24] Cushman D W, Cheung H S 1971 Spectrophotometric assay and properties of the angiotensin-converting enzyme of rabbit lung *Biochem. Pharmacol.* **20** 7 1637-1648
- [25] Ryan J W, Chung A, Ammons C, Carlton M L 1977 A simple radioassay for angiotensin-converting enzyme *Biochem. J.* **167** 2 501-504
- [26] Van Dyeck S, Nováková S, Van Schepdael A, Hoogmartens J 2003 Inhibition study of angiotensin converting enzyme by capillary electrophoresis after enzymatic reaction at capillary inlet *J.*

Chromatogr. A, **1013** 149-156

- [27] Mehanna A S, Dowling M 1999 Liquid chromatographic determination of hippuric acid for the evaluation of ethacrynic acid as angiotensin converting enzyme inhibitor *J. Pharm. Biomed. Anal.* **19** 6 967-973
- [28] Elased K M, Cool D R, Morris M 2005 Novel mass spectrometric methods for evaluation of plasma angiotensin converting enzyme I and renin activity *Hypertension* **46** 4 953-959
- [29] Sentandreu M A, Toldràrapid F 2006 A rapid, simple and sensitive fluorescence method for the assay of angiotensin-I converting enzyme *Food Chem.* **97** 3 546-554
- [30] Wu J, Aluko R E, Nakai S 2006 Structural requirements of angiotensin I-converting enzyme inhibitory peptides: quantitative structure-activity relationship study of di- and tripeptides *J. Agric. Food Chem.* **54** 3 732-738
- [31] Politi A, Dardagi S, Moutevelis-Minakakis P, Kokotos G, Mavromoustakos T 2010 Development of accurate binding affinity predictions of novel renin inhibitors through molecular docking studies *J. Mol. Graph. Model.* **29** 3 425-435
- [32] Meng X Y, Zhang H X, Mezei M, Cui M 2011 Molecular docking: a powerful approach for structure-based drug discovery *Curr. Comput. Drug Des.* **7** 2 146-157
- [33] Wu H, Jiang T, Dong X, Shen G, Li S, Zhang Z 2016 Purification and characterisation of angiotensin-I converting enzyme inhibitory peptides from prickly ash (*Zanthoxylum bungeanum* Maxim) seed proteins hydrolysates *Int. J. Food Eng.* **12** 4 333-34

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