UNIVERSITI PUTRA MALAYSIA

PRODUCTION AND CHARACTERIZATION OF ANGIOTENSIN ICONVERTING ENZYME INHIBITORY PEPTIDES DERIVED FROM ALCALASE-DIGESTED GREEN SOYBEAN [Glycine max (L.) Merr.] PROTEINS

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Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirements for the Degree of Master of Science

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Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirement for the Degree of Master of Science

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Chairman: Professor Nazamid Saari, PhD
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The prevalence of hypertension has escalated to the point where at least a quarter of the world's adult population is afflicted and is projected to increase further. Developing and developed countries are both affected to some extent. Hypertension, by itself or in combination with several other risk factors, presents a formidable challenge to the wellbeing of modern society. However, as a lifestyle-related disease, it can be controlled via modifications to the diet. The research community has undertaken an intensive search for novel compounds able to inhibit the angiotensin I-converting enzyme (ACE), which has been identified as a major target to control hypertension. Synthetic compounds, while effective, has given rise to undesirable side-effects. Therefore, safer alternatives to these compounds have been sought out. ACE inhibitory peptides from food protein sources have been identified as a possible solution. Green soybean (*Glycine max*) has long become a popular food among East Asian countries, but is otherwise not utilized for other purposes. Green soybean has a high protein content (43.35%) which could be exploited to produce bioactive peptides, more specifically, ACE inhibitory peptides. Therefore, the work in this thesis was undertaken to investigate the potential of green soybean to generate ACE inhibitory peptides through enzymatic hydrolysis under controlled conditions. The amino acid content of green soybean was evaluated. Defatted green soybean was hydrolysed by four food-grade proteases namely, Alcalase, Papain, Flavourzyme, and Bromelain, and their hydrolysates' ACE inhibitory activities were compared. The hydrolysate obtained using Alcalase had the strongest inhibitory activity (IC_{50}: 0.14 mg/mL at 6 h hydrolysis time) followed by Papain (IC_{50}: 0.20 mg/mL at 5 h hydrolysis time), Bromelain (IC_{50}: 0.36 mg/mL at 6 h hydrolysis time), and Flavourzyme (IC_{50}: 1.14 mg/mL at 6 h hydrolysis time) hydrolysates. Alcalase-digested hydrolysates were fractionated based on their hydrophobicity using RP-HPLC, and isoelectric points

using isoelectric point focusing technique. The most effective fractions with regards to ACE inhibition were subjected to tandem mass spectrometry for peptide identification. A total of 10 peptides were identified, with five of the peptides being chosen for further characterization based on their ACE inhibitory activities; EAQRLLF, PSLRSYLAE, PDRSIHGRQLAE, FITAFR, and RGQVLS, with IC_{50} values of 878 µM, 532 µM, 1552 µM, 1342 µM, and 993 µM, respectively. The inhibition kinetics of these peptides was studied and a combination of competitive and uncompetitive inhibition modes was found. The results revealed that hydrolysates and peptides with ACE inhibitory activity can be derived from green soybean and might be utilised for development of functional foods with strong antihypertensive activity.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk Ijazah Master Sains

PENGHASILAN DAN PENCIRIAN PEPTIDA PERENCAT ENZIM PENGUBAH ANGIOTENSIN I DARIPADA PROTEIN KACANG SOYA HIJAU [*Glycine max* (L.) Merr.] DICERNA OLEH ALCALASE

Oleh

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Mac 2018

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Kelaziman penyakit hipertensi telah meningkat kepada tahap dimana sekurang-kurangnya satu perempat daripada manusia dewasa seluruh dunia mengalaminya dan jumlah ini dijangka terus meningkat. Kedua-dua jenis negara iaitu yang sedang membangun dan negara maju sama-sama mengalami kesannya. Hipertensi, dengan sendirinya atau digandingkan bersama beberapa faktor risiko lain, adalah satu cabaran yang hebat kepada kesejahteraan masyarakat moden. Walaubagaimanapun, sebagai sebuah penyakit yang berlandaskan gaya hidup, ianya boleh dikawal melalui modifikasi terhadap diet. Komuniti penyelidikan telahpun menjalankan usaha pencarian sebatian novel yang mampu merencat enzim pengubah angiotensin I (ACE), yang telahpun dikenalpasti sebagai sasaran utama untuk mengawal hipertensi. Sebatian sintetik, walaupun terbukti berkesan, mempamerkan kesan sampingan yang tidak diingini. Oleh itu, usaha mencari alternatif yang lebih selamat telah dijalankan. Peptida perencat ACE daripada sumber protein makanan telahpun dikenalpasti sebagai sebuah penyelesaian. Kacang soya hijau (*Glycine max*) telah sekian lama merupakan makanan yang tidak asing dikalangan penduduk negara Asia Timur, namun tidak digunapakai untuk tujuan yang lain. Kacang soya hijau memiliki kandungan protein yang tinggi (43.35%), yang boleh dieksploitasi untuk menghasilkan peptida bioaktif. Oleh itu, tesis ini dijalankan untuk menyiasat potensi kacang soya hijau untuk menghasilkan peptida perencat ACE melalui kaedah hidrolisis enzim di bawah keadaan terkawal. Kandungan asid amino kacang soya hijau telah ditentukan. Kacang soya hijau yang dinyahlemak telah melalui proses hidrolisis oleh empat enzim protease gred makanan iaitu, Alcalase, Papain, Flavourzyme, dan Bromelain, dan kadar aktiviti perencat ACE dalam hidrolisat masing-masing dibandingkan. Hidrolisat yang terhasil menggunakan Alcalase memiliki aktiviti perencatan terbaik (IC_{50}: 0.14 mg/mL pada 6 jam masa hidrolisis) diikuti oleh hidrolisat Papain (IC_{50}: 0.20 mg/mL pada 5 jam masa

hidrolisis), Bromelain (IC_{50}: 0.36 mg/mL pada 5 jam masa hidrolisis) dan Flavourzyme (IC_{50}: 1.14 mg/mL pada 6 jam masa hidrolisis). Hidrolisat yang dihasilkan daripada Alcalase telah dibahagikan berdasarkan tahap hidrofobik menggunakan RP-HPLC, beserta dengan titik isoelektrik menggunakan kaedah pemfokusan titik isoelektrik. Fraksi yang paling berkesan terhadap perencatan ACE telah dipilih untuk pengenalpastian jujukan peptida melalui UPLC-MS/MS. Sebanyak 10 peptida telah dikenalpasti, lima daripadanya dipilih untuk pencirian lanjut berdasarkan aktiviti perencat ACE masing-masing; EAQRLLF, PSLRSYLAE, PDRSIHGRQLAE, FITAFR and RGQVLS, dengan nilai IC_{50} masing-masing sebanyak 878 µM, 532 µM, 1552 µM, 1342 µM, dan 993 µM. Kajian ke atas kinetik perencatan peptida tersebut dijalankan dan gabungan antara mod perencatan kompetitif dan tidak kompetitif dikenalpasti. Hasil kajian menunjukkan hidrolisat serta peptida yang mampu merencat ACE dapat diperoleh dari kacang soya hijau dan seterusnya mungkin dapat digunakan untuk pembangunan makanan fungsian yang memiliki keupayaan antihipertensi yang kuat.

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I certify that a Thesis Examination Committee has met on 5 March 2018 to conduct the final examination of Mohamad Ariff bin Mahlid @ Hanafi on his thesis entitled "Production and Characterization of Angiotensin I-Converting Enzyme Inhibitory Peptides Derived from Alcalase-Digested Green Soybean [*Glycine max* (L.) Merr.] Proteins" in accordance with the Universities and University Colleges Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The Committee recommends that the student be awarded the Master of Science.

Members of the Thesis Examination Committee were as follows:

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This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfilment of the requirement for the degree of Master of Science. The members of the Supervisory Committee were as follows:

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LIST OF ABBREVIATIONS

ACE	Angiotensin I-converting enzyme
gACE	Germinal Angiotensin I-converting enzyme
sACE	Somatic Angiotensin I-converting enzyme
ACN	Acetonitrile
ANOVA	Analysis of variance
AOAC	Association of Official Analytical Chemists
B.C.	Before Christ
°C	Degrees Celsius
Da	Dalton
DH	Degree of hydrolysis
et al.	And others
ESI-Q-TOF	Electrospray ionization-quantitative time-of-flight
FAO	Food and Agriculture Organization of the United Nations
FDA	Food and Drug Administration of the United States
FOSHU	Food for Specified Health Uses
g	Gravity
g	Gram
mg	Miligram
µg	Microgram
h	Hour
HA	Hippuric acid
HCl	Hydrolchloric acid
HHL	Hippuryl-histidine-leucine
HPLC	High performance liquid chromatography
IC_{50}	Half-maximal inhibitory concentration
IEF	Isoelectric focusing
IPG	Immobilised pH Gradient
K_m	Michaelis constant
kV	Kilovolt
L	Liter
mL	Mililiter
µL	Microliter
mm Hg	Millimeter of mercury
mm	Milimeter
µm	Micrometer
nm	Nanometer
mM	Milimolar
µM	Micromolar
min	Minutes
mU	Miliunits
MAFF	Ministry of Agriculture, Forestry and Fisheries, Japan

MAMPU	Malaysian Administrative Modernisation and Management Planning Unit
NCD	Noncommunicable diseases
%	Percentage
p	Probability
pI	Isoelectric point
ppm	Parts per million
PDCAAS	Protein digestibility-corrected amino acid score
QSAR	Quantitative Structure-Activity Relationship
RP-HPLC	Reversed phase high performance liquid chromatography
RPM	Revolutions per minute
TFA	Trifluoroacetic acid
UPLC-MS/MS	Ultra-high performance liquid chromatography-tandem mass spectrometry
v	volume
V	Volt
V_{max}	Maximum enzyme rate of reaction
w	Weight
WHO	World Health Organization
US	United States of America
USDA	United States Department of Agriculture

CHAPTER 1

INTRODUCTION

1.1 Background

Hypertension is a major health problem affecting people from all walks of life and all over the world. It is considered a leading risk factor for mortality (Ezzati, Lopez, Rodgers, Vander, & Murray, 2002) and is projected to affect 1.56 billion individuals by the year 2025 (Kearney et al., 2005). Left untreated, hypertension may lead to other non-commmunicable diseases (NCD) such as stroke, coronary heart disease, kidney dysfunction, disability and death (Lee & Cooper, 2009). Currently, treatment for severe hypertension involves synthetic drugs such as captopril, enalapril, and lisinopril. The aforementioned drugs target a key enzyme in the renin-angiotensin system, the angiotensin I-converting enzyme (ACE), which regulates blood pressure by converting angiotensin I into the potent vasoconstricting angiotensin II, while also inactivating a vasodilator, bradykinin (Erdos, 1975). Therefore, inhibition of ACE results in a decrease of blood pressure. The use of the aforementioned drugs are effective and are supported by clinical trials, but unfortunately cause side-effects such as dry cough, skin rashes, taste disturbances, and angioedema (Roberts, 2014; Messerli, 1999).

ACE inhibitory peptides from food protein sources are considered to be effective and safer without side effects associated with synthetic drugs. A well known example of this is the commercialization of dried bonito hydrolysate, containing ACE inhibitory peptides, which was officially approved as Foods for Specified Health Use (FOSHU) by the Ministry of Health and Welfare in Japan (Ohama, Ikeda, & Moriyama, 2006; Fujita, Yamagami, & Ohshima, 2001). Up until recently, various ACE inhibitory peptides have been identified from different food proteins such as casein (Rahimi et al., 2016; Tauzin, Miclo, & Gaillard 2002; Pihlanto-Leppälä, Rokka, & Korhonen, 1998;), whey protein (Lacroix, Meng, Cheung, & Li-Chan, 2016; Pihlanto-Leppälä et al., 1998), fish proteins (Girgih et al., 2016; Ko et al., 2016; Hwang, 2010; Astawan et al., 1995), algae (Sheih, Fang, & Wu, 2009; Sato et al., 2002; Suetsuna & Chen, 2001), porcine muscles (Katayama et al., 2003; Arihara, Nakashima, Mukai, Ishikawa, & Itoh, 2001), corn gluten (Suh, Whang, Kim, Bae, & Noh, 2003) and soybean (Capriotti et al., 2015; Wu & Ding, 2001; Shin, Ahn, Nam, Lee, & Moon, 1995). Food protein derived ACE inhibitory peptides are promising alternatives to synthetic drugs, as part of a functional food ingredient designed to control hypertension (Li, Le, Shi, & Shrestha, 2004). However, the peptides need to be released from their precursor proteins before being able to express their bioactivity. An appropriate choice of peptide release methodology is needed to fully realise the potential of food proteins to act as a source of ACE inhibitory peptides. Enzymatic hydrolysis are often employed for production of bioactive peptides, due to the degree of control that can be exerted upon the process (Piovesana et al., 2018).

Green soybean or vegetable soybean is a specialty soybean harvested when the seeds are immature (R6 stage), and have expanded to fill 80 to 90 percent of the pod width (Konovsky, Lumpkin, & McClary, 1994). True green soybean varieties are virtually indistinguishable from immature soybeans, other than a few unique characteristics (Mimura, Coyne, Bambuck, & Lumpkin, 2007). Worldwide, it is an underutilized crop but is popular in East Asia especially in Japan and China. As with regular soybeans, green soybean varieties are rich in protein and highly nutritious (Redondo-Cuenca, Villanueva-Suarez, Rodriguez-Sevilla, & Mateos-Aparicio, 2006). The high protein content of green soybean could yield various peptide sequences able to inhibit ACE, thus controlling high blood pressure.

1.2 Problem Statement

Hypertension is a major risk factor for several chronic diseases, and because it is often symptomless, hypertension is considered to be a serious condition requiring medical attention. Hypertension is commonly treated with synthetic drugs, which comes with the risk of adverse side effects, while protein hydrolysates containing peptides with ACE inhibitory activity are considered a safe alternative for human consumption as part of a functional food ingredient. However, the peptides need to be released from its inactive state in their precursor proteins. This often requires the use of certain proteolytic enzymes operating at specific conditions as different enzymes under different conditions produces different peptides with varying degrees of potency against ACE. As noted previously, various types of food protein have been investigated as raw material for production of ACE inhibitory peptides. The continuous search for new sources of ACE inhibitory peptides are based on the need to add value to underutilized resources or food industry byproducts that are rich in protein content (Udenigwe & Aluko, 2012). Green soybean has not been previously assessed for its potential to generate ACE inhibitory peptides. This research attempts to investigate the potential of green soybean as a source of ACE inhibitory peptides due to its status as an underutilized crop.

1.3 Objectives

To the best of my knowledge, green soybean protein has not yet been appraised for its potential ACE inhibitory activity. Thus, in order to evaluate the potential of green soybean as a source of ACE inhibitory peptides, the objectives of this study are (1) to produce protein hydrolysates with ACE inhibitory activity; (2) to fractionate and profile the ACE inhibitory activity of the hydrolysate; and (3) to characterize the mode of action of the ACE inhibitory peptides derived from green soybean protein hydrolysate.

REFERENCES

Acharya, K. R., Sturrock, E. D., Riordan, J. F., & Ehlers, M. R. W. (2003). Ace revisited: A new target for structure-based drug design. *Nature Reviews Drug Discovery*, *2*(11), 891–902.

Astawan, M., Wahyuni, M., Yasuhara, T., Yamada, K., Tadokoro, T., & Maekawa, A. (1995). Effects of angiotensin I-converting enzyme inhibitory substances derived from Indonesian dried-salted fish on blood pressure of rats. *Bioscience, Biotechnology, and Biochemistry*, *59*(3), 425–429.

Abegunde, D. & Stanciole, A. (2006). *An estimation of the economic impact of chronic noncommunicable diseases in selected countries*. Geneva, Switzerland: World Health Organization.

Adam, A., Cugno, M., Molinaro, G., Perez, M., Lepage, Y., & Agostoni, A. (2002). Aminopeptidase P in individuals with a history of angio-oedema on ACE inhibitors. *Lancet*, *359*(9323), 2088–2089.

Adler-Nissen, J. (1986). *Enzymatic hydrolysis of food proteins*. London, England: Elsevier Applied Science Publishers.

Agyei, D. (2015). Bioactive proteins and peptides from soybeans. *Recent Patents on Food, Nutrition & Agriculture*, *7*(2), 100–107.

Aiking, H. (2011). Future protein supply. *Trends in Food Science & Technology*, *22*(2–3), 112–120.

Akillioglu, H. G. & Karakaya, E. S. (2009). Effects of heat treatment and in vitro digestion on the angiotensin converting enzyme inhibitory activity of some legume species. *European Food Research Technology*, *229*(6), 915–921.

Allen, L., Williams, J., Townsend, N., Mikkelsen, B., Roberts, N., Foster, C., & Wickramasinghe, K. (2017). Socioeconomic status and non-communicable disease behavioural risk factors in low-income and lower-middle-income countries: A systematic review. *The Lancet Global Health*, *5*(3), e277–e289.

Aluko, R. E. (2015). Structure and function of plant protein-derived antihypertensive peptides. *Current Opinion in Food Science*, *4*, 44–50.

Al-Kaisi, M., Archontoulis, S., & Kwaw-Mensah, D. (2016). Soybean spatiotemporal yield and economic variability as affected by tillage and crop rotation. *Agronomy Journal*, *108*(3), 1–14.

Association of Official Analytical Chemists. (2005). *Official methods of analysis of AOAC international*. Gaithersburg, MD: Author.

Arai, S., Vattem, D. A., & Kumagai, H. (2016). Functional foods - history and concepts. In D. A. Vattem and V. Maitin (Eds.), *Functional foods, nutraceuticals and natural products: Concepts and applications* (pp. 1–18). Lancaster, PA: DEStech Publications.

Arihara, K., Nakashima, Y., Mukai, T., Ishikawa, T., & Itoh, M. (2001). Peptide inhibitors for angiotensin I-converting enzyme from enzymatic hydrolysates of porcine skeletal muscle proteins. *Meat Science*, *57*(3), 319–324.

Asoodeh, A., Yazdi, M. M., & Chamani, J. (2012). Purification and characterisation of angiotensin I converting enzyme inhibitory peptides from lysozyme hydrolysates. *Food Chemistry*, *131*(1), 291–295.

Banerji, A., Clark, S., Blanda, M., LoVecchio, F., Snyder, B., & Camargo Jr, C. A. (2008). Multicenter study of patients with angiotensin converting enzyme inhibitor–induced angioedema who present to the emergency department. *Annals of Allergy, Asthma & Immunology*, *100*(4), 327–332.

Barbana, C. & Boye, J. I. (2011). Angiotensin I-converting enzyme inhibitory properties of lentil protein hydrolysates: Determination of the kinetics of inhibition. *Food Chemistry*, *127*(1), 94–101.

Beaglehole, R. & Yach, D. (2003). Globalisation and the prevention and control of non-communicable disease: the neglected chronic diseases of adults. *Lancet*, *362*(9387), 903–908.

Bicket, D. P. (2002). Using ACE inhibitors appropriately. *American Family Physician*, *66*(3), 461–468.

Boschin, G., Scigliuolo, G. M., Resta, D. & Arnoldi, A. (2014). ACE-inhibitory activity of enzymatic protein hydrolysates from lupin and other legumes. *Food Chemistry*, *145*, 34–40.

Boye, J. I., Roufik, S., Pesta, N., & Barbana, C. (2010). Angiotensin I-converting enzyme inhibitory properties and SDS-PAGE of red lentil protein hydrolysates. *LWT-Food Science and Technology*, *43*(6), 987-991.

Brew, K. (2003). Structure of human ACE gives new insights into inhibitor binding and design. *Trends in Pharmacological Sciences*, *24*(8), 391–394.

Byun, H. G. & Kim, S. K. (2001). Purification and characterization of angiotensin I-converting enzyme (ACE) inhibitory peptides from Alaska Pollack (*Theragra chalcogramma*) skin. *Process Biochemistry*, *36*(12), 1155–1162.

Campos, M. R. S., González, F. P., Guerrero, L. P., & Ancona, D. B. (2013). Angiotensin I-converting enzyme inhibitory peptides of chia (*Salvia hispanica*) produced by enzymatic hydrolysis. *International Journal of Food Science*, *2013*, 1–8. doi: 10.1155/2013/158482

Capriotti, A. L., Caruso, G., Cavaliere, C., Samperi, R., Ventura, S., Chiozzi, R. Z., & Laganà, A. (2015). Identification of potential bioactive peptides generated by simulated gastrointestinal digestion of soybean seeds and soy milk proteins. *Journal of Food Composition and Analysis*, *44*, 205–213.

Caldwell, P. R., Seegal, B. C., Hsu, K. C., Das, M., & Soffer, R. L. (1976). Angiotensin-converting enzyme: Vascular endothelial localization. *Science*, *191*(4231), 1050–1051.

Carrasco-Castilla, J., Hernández-Álvarez, A. J., Jiménez-Martínez, C., Gutiérrez-López, G. F., Dávila-Ortiz, G. (2012). Use of proteomics and peptidomics methods in food bioactive peptide science and engineering. *Food Engineering Reviews*, *4*(4), 224–243.

Cencic, A. & Chingwaru, W. (2010). The role of functional foods, nutraceuticals, and food supplements in intestinal health. *Nutrients*, *2*(6), 611–625.

Chalé, F. G. H., Ruiz, J. C. R., Fernández, J. J. A., Ancona, D. A. B., & Campos, M. R. S. (2014). ACE inhibitory, hypotensive and antioxidant peptide fractions from *Mucuna pruriens* proteins. *Process Biochemistry*, *49*(10), 1691–1698.

Chel-Guerrero, L., Domínguez-Magaña, M., Martínez-Ayala, A., Dávila-Ortiz, G., & Betancur-Ancona, D. (2012). Lima bean (*Phaseolus lunatus*) protein hydrolysates with ACE-I inhibitory activity. *Food and Nutrition Sciences*, *3*(4), 511–521.

Chen, J. R., Okada, T., Muramoto, K., Suetsuna, K., & Yang, S. C. (2002). Identification of angiotensin I-converting enzyme inhibitory peptides derived from the peptic digest of soybean protein. *Journal of Food Biochemistry*, *26*(6), 543–554.

Cheung, H. S., Wang, F. L., Ondetti, M. A., Sabo, E. F., & Cushman, D. W. (1980). Binding of peptide substrates and inhibitors of angiotensin-converting enzyme. Importance of the COOH- terminal dipeptide sequence. *Journal of Biological Chemistry*, *255*(2), 401–407.

Chiang, W., Tsou, M., Tsai, Z., & Tsai, T. (2006). Angiotensin I-converting enzyme inhibitor derived from soy protein hydrolysate and produced by using membrane reactor. *Food Chemistry*, *98*(4), 725–732.

Cinq-Mars, C. D., Hu, H., Kitts, D. D., & Li-Chan, E. C. Y. (2008). Investigations into inhibitor type and mode, simulated gastrointestinal digestion, and cell transport of the angiotensin I-converting enzyme–inhibitory peptides in Pacific Hake (*Merluccius productus*) fillet hydrolysate. *Journal of Agricultural and Food Chemistry*, *56*(2), 410–419.

Clare, D. A., & Swaisgood, H. E. (2000). Bioactive milk peptides: A prospectus. *Journal of Dairy Science*, *83*(6), 1187–1195.

Clemente, A. (2000). Enzymatic protein hydrolysates in human nutrition. *Trends in Food Science & Technology*, *11*(7), 254–262.

Cooper, W. O., Hernandez-Diaz, S., Arbogast, P. G., Dudley, J. A., Dyer, S., Gideon, P. S., . . . Ray, W. A. (2006). Major congenital malformations after first-trimester exposure to ACE inhibitors. *The New England Journal of Medicine*, *354*(23), 2443–2451.

Copeland, R. A. (2013a). Enzyme reaction mechanisms. *Evaluation of enzyme inhibitors in drug discovery: A guide for medicinal chemists and pharmacologists*. (pp. 25–55). Hoboken, NJ: Wiley.

Copeland, R. A. (2013b). Reversible modes of inhibitor interactions with enzymes. *Evaluation of enzyme inhibitors in drug discovery: A guide for medicinal chemists and pharmacologists*. (pp. 57–121). Hoboken, NJ: Wiley.

Cruz, J. N. D., Pimenta, D. C., Melo, R. L. D., & Nascimento, J. R. O. (2016). Isolation and biochemical characterisation of angiotensin-converting enzyme inhibitory peptides derived from the enzymatic hydrolysis of cupuassu seed protein isolate. *Journal of Functional Foods*, *27*, 104–114.

Cushman, D. W., Cheung, H. S., Sabo, E. F., & Ondetti, M. A. (1977). Design of potent competitive inhibitors of angiotensin-converting enzyme. Carboxyalkanoyl and mercaptoalkanoyl amino acids. *Biochemistry*, *16*(25), 5484–5491.

Cushman, D. & Cheung, H. (1971). Inhibition of homogeneous angiotensin I-converting enzyme of rabbit lung by synthetic venom peptides of *Bothrops jararaca*. *Biochimica et Biophysica Acta*, *293*(2), 451–463.

De Boer, J. & Aiking, H. (2011). On the merits of plant-based proteins for global food security: Marrying macro and micro perspectives. *Ecological Economics*, *70*(7), 1259–1265.

Dicpinigaitis, P. V. (2006). Angiotensin-converting enzyme inhibitor-induced cough. *CHEST*, *129*, 169S–173S.

Dorer, F. E., Kahn, J. R., Lentz, K. E., Levine, M., & Skeggs, L. T. (1974). Hydrolysis of bradykinin by angiotensin-converting enzyme. *Circulation Research*, *34*(6), 824–827.

Duppong, L. M., & Hatterman-Valenti, H. (2005). Yield and quality of vegetable soybean cultivars for production in North Dakota. *HortTechnology*, *15*(4), 896–900.

Erdman, Jr, J. W. & Fordyce, E. J. (1989). Soy products and the human diet. *American Journal of Clinical Nutrition*, *49*(5), 725–737.

Erdos, E. G. (1975). Angiotensin I-converting enzyme. *Circulation Research*, 36(2), 247–255.

Ezzati, M., Lopez, A. D., Rodgers, A., Vander, H. S., & Murray, C. J. (2002). Selected major risk factors and global and regional burden of disease. *Lancet*, *360*(9343), 1347–1360.

Food and Agriculture Organization. (1991). *Protein quality evaluation in human diets. Report of joint FAO/WHO expert consultation*. (FAO Food and Nutrition Paper No. 51). Rome, Italy: Author.

Food and Drug Administration. (1999). Food labeling: Health claims; soy protein and coronary heart disease. final rule. *Federal Register*, *64*: 57700–57733.

Ferrario, M. (2009). Role of angiotensin II in cardiovascular disease – therapeutic implications of more than a century of research. *Journal of the Renin-Angiotensin-Aldosterone System*, *7*(1), 3–14.

Flather, M. D., Yusuf, S., Køber, L., Pfeffer, M., Hall, A., Murray, G., … Braunwald, E. (2000). Long-term ACE-inhibitor therapy in patients with heart failure or left-ventricular dysfunction: A systematic overview of data from individual patients. *Lancet*, *355*(9215), 1575–1581.

Forghani, B., Ebrahimpour, A., Bakar, J., Hamid. A. A., Hassan, Z., & Saari, N. (2012). Enzyme hydrolysates from *Stichopus horrens* as a new source for angiotensin-converting enzyme inhibitory peptides. *Evidence-Based Complementary and Alternative Medicine*, *2012*, 1–9. doi:10.1155/2012/236384

Forghani, B., Zarei, M., Ebrahimpour, A., Philip, R., Bakar, J., Hamid. A. A., & Saari, N. (2016). Purification and characterization of angiotensin converting enzyme-inhibitory peptides derived from *Stichopus horrens*: Stability study against the ACE and inhibition kinetics. *Journal of Functional Foods*, *20*, 276–290.

Forouzanfar, M. H., Liu, P., Roth, G. A., Ng, M., Biryukov, S., Marczak, L., . . . Murray, C. J. L. (2017). Global burden of hypertension and systolic blood pressure of at least 110 to 115 mm Hg, 1990-2015. *JAMA*, *317*(2), 165–182.

Frieden, T. R. & Jaffe, M. G. (2018). Saving 100 million lives by improving global treatment of hypertension and reducing cardiovascular disease risk factors. *Journal of Clinical Hypertension*, *20*(2), 208–211.

Fujita, H., & Yoshikawa, M. (1999). LKPNM: A prodrug-type ACE inhibitory peptide derived from fish protein. *Immunopharmacology*, *44*(1–2), 123–127.

Fujita, H., Yokoyama, K., & Yoshikawa, M. (2000). Classification and antihypertensive activity of angiotensin I-converting enzyme inhibitory peptides derived from food proteins. *Journal of Food Science*, *65*(4), 564–569.

Fujita, H., Yamagami, T., & Ohshima, K. (2001). Effects of an ACE inhibitory agent, katsuobushi oligopeptide, in the spontaneously hypertensive rat and in borderline and mildly hypertensive subjects. *Nutrition Research*, *21*(8), 1149–1158.

Fukushima, D. (2001). Recent progress in research and technology on soybeans. *Food Science and Technology Research*, *7(*1), 8–16.

García, N. C., Endermann, J., González-García, E., & Marina, M. L. (2015). HPLC-Q-TOF-MS identification of antioxidant and antihypertensive peptides recovered from cherry (*Prunus cerasus* L.) subproducts. *Journal of Agricultural and Food Chemistry*, *63*(5), 1514–1520.

Garcia-Mora, P., Frias, J., Peñas, E., Zielinski, H., Giménez-Bastida, J., A., Wiczkowski, W., . . . Martínez-Villaluenga, C. (2015). Simultaneous release of peptides and phenolics with antioxidant, ACE-inhibitory and anti-inflammatory activities from pinto bean (*Phaseolus vulgaris* L. var. pinto) proteins by subtilisins. *Journal of Functional Foods*, *18*(Part A), 319–332.

Gavras, H. & Gavras, I. (1988). Angiotensin converting enzyme inhibitors. Properties and side effects. *Hypertension*, *11*(3 Part II), II37–II39.

Gibbs, B. F., Zougman, A., Masse, R., & Mulligan, C. (2004). Production and characterization of bioactive peptides from soy hydrolysate and soy-fermented food. *Food Research International*, *37*(2), 123–131.

Girgih, A. T., Nwachukwu, I. D., Hasan, F. M., Fagbemi, T. N., Malomo, S. A., Gill, T. A., & Aluko, R. E. (2016). Kinetics of in vitro enzyme inhibition and blood pressure-lowering effects of salmon (*Salmo salar*) protein hydrolysates in spontaneously hypertensive rats. *Journal of Functional Foods*, *20*, 43– 53.

Gobbeti, M., Ferranti, P., Smacchi, E., Goffredi, F., & Addeo, F. (2000). Production of angiotensin-I-converting-enzyme-inhibitory peptides in fermented milk started by *Lactobacillus delbrueckii* subsp. *Bulgaricus* SS1 and *Lactococcus lactis* subsp. *Cremoris* FT4. *Applied and Environmental Microbiogy*, *66*(9), 3898–3904.

Goryakin, Y., Rocco, L., & Suhrcke, M. (2017). The contribution of urbanization to non-communicable diseases: Evidence from 173 countries from 1980 to 2008. *Economics & Human Biology*, *26*, 151–163.

Gu, Y. & Wu, J. (2013). LC–MS/MS coupled with QSAR modeling in characterising of angiotensin I-converting enzyme inhibitory peptides from soybean proteins. *Food Chemistry*, *141*(3), 2682–2690.

Guan, H. L., Guo, W. L., Huan, L., & Yong, H. S. (2005). Mungbean protein hydrolysates obtained with Alcalase exhibit angiotensin I-converting enzyme inhibitory activity. *Food Science and Technology International*, *11*(4), 281–287.

Guang, C. & Phillips, R. D. (2009). Plant food-derived angiotensin I converting enzyme inhibitory peptides. *Journal of Agricultural and Food Chemistry*, *57*(12), 5113–5120.

Guang, C., Phillips, R. D., Jiang, B., & Milani, F. (2012). Three key proteases–angiotensin-I-converting enzyme (ACE), ACE2 and renin–within and beyond the renin-angiotensin system. *Archives of Cardiovascular Disease*, *105*(6–7), 373–385.

Guo, Y., Pan, D., & Tanokura, M. (2009). Optimisation of hydrolysis conditions for the production of the angiotensin-I converting enzyme (ACE) inhibitory peptides from whey protein using response surface methodology. *Food Chemistry*, *114*(1), 328–333.

Graham, H. & Vance, C. P. (2003). Legumes: Importance and constraints to greater use. *Plant Physiology*, *131*(3), 872–877.

Hagaman, J. R., Moyer, J. S., Bachman, E. S., Sibony, M., Magyar, P. L., Welch, J. E., . . . O'Brien, D. A. (1998). Angiotensin-converting enzyme and male fertility. *Medical Sciences*, *95*(5), 2552–2557.

Han, S. W., Chee, K. M., & Cho S. J. (2015). Nutritional quality of rice bran protein in comparison to animal and vegetable protein. *Food Chemistry*, *172*(1), 766–769.

Hartmann, R. & Meisel, H. (2007). Food-derived peptides with biological activity: from research to food applications. *Current Opinion in Biotechnology*, *18*(2), 163–169.

Hernández-Álvarez, A. J., Carrasco-Castilla, J., Dávila-Ortiz, G., Alaiz, M., Girón-Calle, J., Vioque-Peña, J., . . . Jiménez-Martínez, C. (2012). Angiotensin-converting enzyme-inhibitory activity in protein hydrolysates from normal and anthracnose disease-damaged *Phaseolus vulgaris* seeds. *Journal of the Science of Food and Agriculture*, *93*(4), 961–966.

Hernández-Ledesma, B., Contreras, M. D. M., & Recio, I. (2011). Antihypertensive peptides: Production, bioavailability and incorporation into foods. *Advances in Colloid and Interface Science*, *165*(1), 23–35.

Hou, Y. & Zhao, X. H. (2011). Limited hydrolysis of two soybean protein products with trypsin or neutrase and the impacts on their solubility, gelation, and fat absorption capacity. *Biotechnology*, *10*(2), 190–196.

Hrckova, M., Rusnakova, M., & Zemanovic, J. (2002). Enzymatic hydrolysis of defatted soy flour by three different proteases and their effect on the functional properties of resulting protein hydrolysates. *Czech Journal of Food Science*, *20*(1), 7–14.

Hwang, J. S. (2010). Impact of processing on stability of angiotensin I-converting enzyme (ACE) inhibitory peptides obtained from tuna cooking juice. *Food Research International*, *43*(3), 902–906.

Hymowitz, T. (1990). Soybeans: The success story. In J. Janick and J. E. Simon (Eds.), *Advances in new crops* (pp. 159–163). Portland, OR: Timber Press.

Iqbal, A., Khalil, I. A., Ateeq, N., & Khan, M. S. (2006). Nutritional quality of important food legumes. *Food Chemistry*, *97*(2), 331–335.

Iwaniak, A., Minkiewicz, P., & Darewicz, M. (2014). Food-originating ACE inhibitors, including antihypertensive peptides, as preventive food components in blood pressure reduction. *Comprehensive Reviews in Food Science and Food Safety*, *13*(2), 114–134.

Jakubczyk, A., & Baraniak, B. (2014). Angiotensin I converting enzyme inhibitory peptides obtained after in vitro hydrolysis of pea (*Pisum sativum* var. Bajka) globulins. *BioMed Research International*, *2014*, 1–8. doi: 10.1155/2014/438459

Jao, C. L., Huang, S. L., & Hsu, K. C. (2012). Angiotensin I-converting enzyme inhibitory peptides: Inhibition mode, bioavailability, and antihypertensive effects. *BioMedicine*, *2*(4), 130–136.

Jimsheena, V. K. & Gowda, L. R. (2009). Colorimetric, high-throughput assay for screening angiotensin I-converting enzyme inhibitors. *Analytical Chemistry*, *81*(22), 9388–9394.

Jimsheena, V. K. & Gowda, L. R. (2011). Angiotensin I-converting enzyme (ACE) inhibitory peptides derived from arachin by simulated gastric digestion. *Food Chemistry*, *125*(2), 561–569.

Junot, C., Gonzales, M. C., Ezan, E., Cotton, J., Vazeux, G., Michaud, A., . . . Dive, V. (2001). RXP 407, a selective inhibitor of the N-domain of angiotensin I-converting enzyme, blocks in vivo the degradation of hemoregulatory peptide acetyl-Ser-Asp-Lys-Pro with no effect on angiotensin I hydrolysis. *Journal of Pharmacology and Experimental Therapeutics*, *297*(2), 606–611.

Kapel, R., Rahhou, E., Lecouturier, D., Guillochon, D., & Dhulster, P. (2006). Characterization of an antihypertensive peptide from an Alfalfa white protein hydrolysate produced by a continuous enzymatic membrane reactor. *Process Biochemistry*, *41*(9), 1961–1966.

Katayama, K., Fuchu, H., Sakata, A., Kawahara, S., Yamauchi, K., Kawamura, Y., & Muguruma, M. (2003). Angiotensin I-converting enzyme inhibitory activities of porcine skeletal muscle proteins following enzyme digestion. *Asian-Australasian Journal of Animal Sciences*, *16*(3), 417–424.

Kaviani, B. & Kharabian, A. (2008). Improvement of the nutritional value of soybean [*Glycine max* (L) Merr.] seed with alteration in protein subunits of glycinin (11S globulin) and β-conglycinin (7S globulin). *Turkish Journal of Biology*, *32*, 91–97.

Kearney, P. M., Whelton, M., Reynolds, K., Muntner, P., Whelton, P. K. & He, J. (2005). Global burden of hypertension: Analysis of worldwide data. *Lancet*, *365*(9455), 217–223.

Kim, J. M., Whang, J. H., & Suh, H. J. (2004). Enhancement of angiotensin I converting enzyme inhibitory activity and improvement of the emulsifying and foaming properties of corn gluten hydrolysate using ultrafiltration membranes. *European Food Research and Technology*, *218*(2), 133–138.

Ko, S. C., Lee, J. K., Byun, H. G., Lee, S. C., & Jeon, Y. J. (2012). Purification and characterization of angiotensin I-converting enzyme inhibitory peptide from enzymatic hydrolysates of *Styela clava* flesh tissue. *Process Biochemistry*, *47*(1), 34–40.

Ko, J. Y., Kang, N., Lee, J. H., Kim, J. S., Kim, W. S., Park, S. J., . . . Jeon, Y. J. (2016). Angiotensin I-converting enzyme inhibitory peptides from an enzymatic hydrolysate of flounder fish (*Paralichthys olivaceus*) muscle as a potent anti-hypertensive agent. *Process Biochemistry*, *51*(4), 535–541.

Konovsky, J., Lumpkin, T. A., & McClary, D. (1994). Edamame: The vegetable soybean. In A. D. O'Rourke (Ed.), *Understanding the Japanese food and agrimarket: A multifaceted opportunity* (pp. 173–181). Binghamton, NY: Haworth Press.

Kontis, V., Mathers, C. D., Rehm, J., Stevens, G. A., Shield, K. D., Bonita, R., . . . Ezzati, M. (2014). Contribution of six risk factors to achieving the 25×25 non-communicable disease mortality reduction target: A modelling study. *Lancet*, *384*(9941), 427–437.

Kostis, J. B., Shelton, B., Gosselin, G., Goulet, C., Hood, Jr., W. B., Kohn, R. M., . . . Probstfield, J. (1996). Adverse effects of enalapril in the studies of left ventricular dysfunction (SOLVD). *American Heart Journal*, *131*(2), 350–355.

Krishnan, H. B., Natarajan, S.S., Mahmoud, A.A., & Nelson, R. L. (2007). Identification of Glycinin and *β*-conglycinin Subunits that contribute to the increased protein content of high-protein soybean lines. *Journal of Agricultural and Food Chemistry*, *55*(5), 1839–1845.

Kuba, M., Tanaka, K., Tawata, S., Takeda, Y., & Yasuda, M. (2003). Angiotensin I-converting enzyme inhibitory peptides isolated from tofuyo fermented soybean food. *Bioscience, Biotechnology, and Biochemistry*, *67*(6), 1278–1283.

Lacroix, I. M. E., Meng, G., Cheung, I. W. Y., & Li-Chan, E. C. Y. (2016). Do whey protein-derived peptides have dual dipeptidyl-peptidase IV and angiotensin I-converting enzyme inhibitory activities? *Journal of Functional Foods*, *21*, 87–96.

Le Cotty, T. & Dorin, B. (2012). A global foresight on food crop needs for livestock. *Animal*, *6*(9), 1528–1536.

Lee, D. E. & Cooper, R. S. (2009). Recommendations for global hypertension monitoring and prevention. *Current Hypertension Reports*, *11*, 444–449.

L'hocine, L., Boye J. I., & Arcand, Y. (2006). Composition and functional properties of soy protein isolates prepared using alternative defatting and extraction procedures. *Journal of Food Science*, *71*(3), C137–C145.

Li-Chan, E. C. Y. (2015). Bioactive peptides and protein hydrolysates: research trends and challenges for application as nutraceuticals and functional food ingredients. *Current Opinion in Food Science*, *1*, 28–37.

Li, G. H., Le, G. W., Shi, Y. H., & Shrestha, S. (2004). Angiotensin I-converting enzyme inhibitory peptides derived from food proteins and their physiological and pharmacological effects. *Nutrition Research*, *27*(7), 469–486.

Li, G. H., Wan, J. Z., Le, G. W., & Shi, Y. H. (2006). Novel angiotensin I-converting enzyme inhibitory peptides isolated from alcalase hydrolysate ofmung bean protein. *Journal of Peptide Science*, *12*(8), 509–514.

Li, G. H., Shi, Y. H., Liu, H., & Le, G. W. (2006). Antihypertensive effect of alcalase generated mung bean protein hydrolysates in spontaneously hypertensive rats. *European Food Research and Technology*, *222*(5–6), 733–736.

Lieske, B. & Konrad, G. (1994). Protein hydrolysis–the key to meat flavoring systems. *Food Reviews International*, *10*(3), 287–312.

Liu, H., Le, G. W., Shi, Y. H., & Li, G. H. (2005). Structural parameterization and QSAR of angiotensin I-converting enzyme inhibitory tripeptides. *Computers and Applied Chemistry*, *22*, 732–738.

Liu, X., Zhang, M., Jia, A., Zhang, Y., Zhu, H., Zhang, C., . . . Liu, C. (2013a). Purification and characterization of angiotensin I converting enzyme inhibitory peptides from jellyfish *Rhopilema esculentum*. *Food Research International*, *50*(1), 339–343.

Liu, M., Du, M., Zhang, Y., Xu, W., Wang, C., Wang, K., & Zhang, L. (2013b). Purification and identification of an ACE inhibitory peptide from walnut protein. *Journal of Agricultural and Food Chemistry*, *61*(17), 4097–4100.

Luis, C. G., Mario, D. M., Alma, M. A., Gloria, D. O., & David, B. A. (2012). Lima bean (*Phaseolus lunatus*) protein hydrolysates with ACE-I inhibitory activity. *Food and Nutrition Sciences*, *3*(4), 511–521.

Lule, V. K., Garg, S., Pophaly, S. D., Hitesh, & Tomar, S. K. (2015). Potential health benefits of Lunasin: A multifaceted soy-derived bioactive peptide. *Journal of Food Science*, *80*(3), R485–R494.

Luna-Vital, D. A., Mojica, L., de Mejía, E. G., Mendoza, S., & Loarca-Piña, G. (2015). Biological potential of protein hydrolysates and peptides from common bean (*Phaseolus vulgaris* L.): A review. *Food Research International*, *76*(Part 1), 39–50.

Ministry of Agriculture, Forestry and Fisheries. (2014). *The 89th statistical yearbook of Ministry of Agriculture, Forestry and Fisheries (2013–2014)*. Retrieved from http://www.maff.go.jp/e/tokei/kikaku/nenji_e/89nenji/index.html

Majumder, K. & Wu, J. (2010). A new approach for identification of novel antihypertensive peptides from egg proteins by QSAR and bioinformatics. *Food Research International*, *43*(5), 1371–1378.

Mala, B. R., Aparna, M. T., Mohini, S. G., & Vasanti, V. D. (1998). Molecular and biotechnological aspects of microbial proteases. *Microbial and Molecular Biology Reviews*, *62*(3), 597–635.

Mallikarjun Gouda, K. G., Gowda, L. R., Rao, A. G., & Prakash, V. (2006). Angiotensin I-converting enzyme inhibitory peptide derived from glycinin, the 11S globulin of soybean (*Glycine max*). *Journal of Agricultural and Food Chemistry*, *54*(13), 4568–4573.

Masuda, R. (1991). Quality requirement and improvement of vegetable soybean. In S. Shanmugasundaram (Ed.), *Vegetable soybean: Research needs for production and quality improvement*. Paper presented at a workshop of the Asian Vegetable Research and Development Center, Kenting, Taiwan. (pp. 92–102). Taipei: Asian Vegetable Research and Development Center.

Matsui, T., Li, C. H., & Osajima, Y. (1999). Preparation and characterization of novel bioactive peptides responsible for angiotensin I-converting enzyme inhibition from wheat germ. *Journal of Peptide Science*, *5*(7), 289–297.

Messerli, F. H. (1999). Combinations in the treatment of hypertension: ACE inhibitors and calcium antagonists. *American Journal of Hypertension*, *12*, 86S–90S.

Millward, D. J., Layman, D. K., Tomé, D., & Schaafsma, G. (2008). Protein quality assessment: impact of expanding understanding of protein and amino acid needs for optimal health. *The American Journal of Clinical Nutrition*, *87*(5), 1576S–1581S.

Mimura, M., Coyne, C. J., Bambuck, M. W. & Lumpkin, T. A. (2007). SSR diversity of vegetable soybean [*Glycine max* (L.) Merr.]. *Genetic Resources and Crop Evolution*, *54*(3), 497–508.

Min, C. W., Gupta, R., Kim, S. W., Lee, S. E., Kim, Y. C., Bae, D. W., . . . Kim, S. T. (2015). Comparative biochemical and proteomic analyses of soybean seed cultivars differing in protein and oil content. *Journal of Agricultural and Food Chemistry*, *63*(32), 7134–7142.

Mullally, M. M., Meisel, H., & FitzGerald, R. J. (1997). Angiotensin I-converting enzyme inhibitory activities of gastric and pancreatic proteinase digests of whey proteins. *International Dairy Journal*, *7*(5), 299–303.

Murray, B. A. & FitzGerald, R. J. (2007). Angiotensin converting enzyme inhibitory peptides derived from food proteins: biochemistry, bioactivity and production. *Current Pharmaceutical Design*, *13*(8), 773–791.

Natarajan, S. S. (2014). Analysis of soybean seed proteins using proteomics. *Journal of Data Mining in Genomics & Proteomics*, *5*(1), 1–3.

Natesh, R., Schwager, S. L. U., Sturrock, E.D., & Acharya, K. R. (2003). Crystal structure of the human angiotensin-converting enzyme-lisinopril complex. *Nature*, *421*, 551–554.

Nchienzia, H. A., Morawicki, R. O., & Gadang, V. P. (2010). Enzymatic hydrolysis of poultry meal with endo- and exopeptidases. *Poultry Science*, *89*(10), 2273–2280.

Ni, H., Li, L., Liu, G., & Hu, S. Q. (2012). Inhibition mechanism and model of an angiotensin I-converting enzyme (ACE)-inhibitory hexapeptide from yeast (*Saccharomyces cerevisiae*). *PLoS ONE*, *7*(5), 1–7. doi: 10.1371/journal.pone.0037077

Nielsen, P. M., Petersen, D., & Dambmann, C. (2001). Improved method for determining food protein degree of hydrolysis. *Journal of Food Science*, *66*(5), 642–646.

Norris, R., Casey, F., FitzGerald R. J., Shields, D., & Mooney C. (2012). Predictive modelling of angiotensin converting enzyme inhibitory dipeptides. *Food Chemistry*, *133*(4), 1349–1354.

Ohama, H., Ikeda, H., & Moriyama H. (2006). Health foods and foods with health claims in Japan. *Toxicology*, *221*(1), 95–111.

Ondetti, M. A., Rubin, B., & Cushman, D. W. (1977). Design of specific inhibitors of angiotensin-converting enzyme: New class of orally active antihypertensive agents. *Science, 196*(4288), 441–444.

Ondetti, M. A. & Cushman, D. W. (1982). Enzymes of the rennin-angiotensin system and their inhibitors. *Annual Review in Biochemistry, 51*, 283–308.

Pan, D., Cao, J., Guo, H., & Zhao, B. (2012). Studies on purification and the molecular mechanism of a novel ACE inhibitory peptide from whey protein hydrolysate. *Food Chemistry*, *130*(1), 121–126.

Panyam, D. & Kilara, A. (1996). Enhancing the functionality of food proteins by enzymatic modification. *Trends in Food Science & Technology*, *7*(4), 120–125.

Pedroche, J., Yust, M. M., Girón-Calle, J., Alaiz, M., Millán, F., & Vioque, J. (2002). Utilization of chickpea protein isolates for production of peptides with angiotensin I-converting enzyme (ACE)-inhibitory activity. *Journal of the Science of Food and Agriculture, 82*(9), 960–965.

Pihlanto-Leppälä, A., Rokka, T., & Korhonen, H. (1998). Angiotensin I-converting enzyme inhibitory peptides derived from bovine milk proteins. *International Dairy Journal*, *8*(4), 325–331.

Pihlanto, A., Akkanen, S., & Korhonen, H. J. (2008). ACE inhibitory and antioxidant properties of potato (*Solanum tuberosum*). *Food Chemistry, 109*(1), 104–112.

Piovesana, S., Capriotti, A. L., Cavaliere, C., Barbera, G. L., Montone, C. M., Chiozzi, R. Z., & Laganà, A. (2018). Recent trends and analytical challenges in plant bioactive peptide separation, identification and validation. *Analytical and Bioanalytical Chemistry*, *2018*, 1–20. doi: 10.1007/s00216-018-0852-x

Ponnusha B. S., Subramaniyam S., Pasupathi P., Subramaniyam B., & Virumandy, R. (2011). Antioxidant and Antimicrobial properties of *Glycine max*-A review. *International Journal of Current Biological and Medical Science, 1*(2), 49–62.

Pripp, A. H, Isaksson, T., Stepaniak, L., Sørhaug, T., & Ardö, Y. (2005). Quantitative structure activity relationship modeling of peptides and proteins as a tool in food science. *Trends in Food Science & Technology*, *16*(11), 484–494.

Quist, E. E., Phillips, R. D., & Saalia, F. K. (2009). Angiotensin converting enzyme inhibitory activity of proteolytic digests of peanut (*Arachis hypogaea* L.). *Food Science and Technology*, *42*(3), 694-699.

Rahimi, M., Ghaffari, S. M., Salami, M., Mousavy, S. J., Niasari-Naslaji, A., Jahanbani, R., . . . Moosavi-Movahedi, A. A. (2016). ACE-inhibitory and radical scavenging activities of bioactive peptides obtained from camel milk casein hydrolysis with proteinase K. *Dairy Science & Technology*, *96*(4), 489–499.

Rayaprolu, S. J., Hettiarachchy, N. S., Chen, P., Kannan, A., & Mauromostakos, A. (2013). Peptides derived from high oleic acid soybean meals inhibit colon, liver and lung cancer cell growth. *Food Research International*, *50*(1), 282–288.

Redondo-Cuenca, A., Villanueva-Suarez, M. J., Rodriguez-Sevilla, M. D. & Mateos-Aparicio, I. (2006). Chemical composition and dietary fibre of yellow and green commercial soybeans (*Glycine max*). *Food Chemistry, 101*(3), 1216–1222.

Ren, S. C., Liu, Z. L., & Wang, P. (2012). Proximate composition and flavonoids content and in vitro antioxidant activity of 10 varieties of legume seeds grown in China. *Journal of Medicinal Plants Research*, *6*(2), 301–308.

Riordan, J. F. (2003). Angiotensin-I-converting enzyme and its relatives. *Genome Biology*, 4(8), 1–5.

Roberts, J. R. (2014). Potentially fatal side effect of ACE inhibitors: Angioedema. *Emergency Medicine News*, *36*(3), 8–11.

Roy, F., Boye, J. I., & Simpson, B. K. (2010). Bioactive proteins and peptides in pulse crops: Pea, chickpea and lentil. *Food Research International*, *43*(2), 432–442.

Rui, X., Boye, J. I., Simpson, B. K., & Prasher, S. O. (2012). Angiotensin I-converting enzyme inhibitory properties of *Phaseolus vulgaris* bean hydrolysates: Effects of different thermal and enzymatic digestion treatments. *Food Research International*, *49*(2), 739–746.

Rui, X., Boye, J. I., Simpson, B. K., & Prasher, S. O. (2013). Purification and characterization of angiotensin I-converting enzyme inhibitory peptides of small red bean (*Phaseolus vulgaris*) hydrolysates. *Journal of Functional Foods*, *5*(3), 1116–1124.

Sagardia, I., Roa-Ureta, R. H., & Bald, C. (2013). A new QSAR model, for angiotensin I-converting enzyme inhibitory oligopeptides. *Food Chemistry*, *136*(3–4), 1370–1376.

Sato, M., Oba, T., Yamaguchi, T., Nakano, T., Kahara, T., Funayama, K., . . . Nakano, T. (2002). Antihypertensive effects of hydrolysates of wakame (*Undaria pinnatifida*) and their angiotensin I-converting enzyme inhibitory activity. *Annals of Nutrition & Metabolism*, *46*(6), 259–267.

Sentandreu, M. A. & Toldrá, F. (2006). A fluorescence-based protocol for quantifying angiotensin-converting enzyme activity. *Nature Protocols*, *1*(5), 2423–2427.

Sheih, I. C., Fang T. J., & Wu, T. K. (2009). Isolation and characterisation of a novel angiotensin I-converting enzyme (ACE) inhibitory peptide from the algae protein waste. *Food Chemistry*, *115*(1), 279–284.

Shin, Z. I., Ahn, C. W., Nam, H. S., Lee, H. J., & Moon, T. H. (1995). Fractionation of angiotensin converting enzyme inhibitory peptide from soybean paste. *Korean Journal of Food Science and Technology*, *27*(2), 230–234.

Shin, Z. I., Yu, R., Park, S. A., Chung, D. K., Ahn, C. W., Nam, H. S., . . . Lee, H. J. (2001). His-His-Leu, an Angiotensin I-converting enzyme inhibitory peptide derived from Korean soybean paste, exerts antihypertensive activity in vivo. *Journal of Agricultural and Food Chemistry*, *49*(6), 3004–3009.

Soffer, R. L. (1976). Angiotensin-converting enzyme and the regulation of vasoactive peptides. *Annual Review of Biochemistry*, *45*, 73–94.

Song, Y. S., Frias, J., Martinez-Villaluenga, C., Vidal-Valdeverde, C., & De Mejia, E. G. (2008). Immunoreactivity reduction of soybean meal by fermentation, effect on amino acid composition and antigenicity of commercial soy products. *Food Chemistry*, *108*(2), 571–581.

Song, J., Liu, C., Li, D., & Gu, Z. (2013). Evaluation of sugar, free amino acid, and organic acid compositions of different varieties of vegetable soybean (*Glycine max* [L.] Merr). *Industrial Crops and Products*, *50*, 743–749.

Steinkraus, K. H. (2002). Fermentations in world food processing. *Comprehensive Reviews in Food Science and Food Safety*, *1*(1), 23–32.

Suetsuna, K., & Chen, J. R. (2001). Identification of antihypertensive peptides from peptic digest of two microalgae, *Chlorella vulgaris* and *Spirulina platensis*. *Marine Biotechnology*, *3*(4), 305–309.

Suetsuna, K., & Nakano, T. (2000). Identification of an antihypertensive peptide from peptic digest of wakame (*Undaria pinnatifida*). *The Journal of Nutritional Biochemistry*, *11*(9), 450–454.

Suh, H. J., Whang, J. H., Kim, Y. S., Bae, S. H., & Noh, D. O. (2003). Preparation of angiotensin I-converting enzyme inhibitor from corn gluten. *Process Biochemistry*, *38*(8), 1239–1244.

Health Canada. (2015). *Summary of Health Canada's assessment of a health claim about soy protein and cholesterol lowering*. Retrieved from https://chfa.ca/images/uploads/2011/11/2015-03-HC-Food-Directorate-Summary-of-Health-Claim-Petition-Soy-Protein-Cholesterol-Lowering.pdf

Tang, C. H., Chen, L., & Ma, C. Y. (2009). Thermal aggregation, amino acid composition and in vitro digestibility of vicilin-rich protein isolates from three *Phaseolus* legumes: A comparative study. *Food Chemistry*, *113*(4), 957–963.

Tauzin, J., Miclo, L., & Gaillard, J. L. (2002). Angiotensin I-converting enzyme inhibitory peptides from tryptic hydrolysate of bovine α_{s2}-casein. *FEBS Letters*, *531*(2), 369–374.

Tiengo, A., Faria, M., & Netto, F. M. (2009). Characterization and ACE- Inhibitory activity of amaranth proteins. *Journal of Food Science*, *74*(5), H121–H126.

Tilman, D., Balzer, C., Hill, J., & Befort, B. L. (2011). Global food demand and the sustainable intensification of agriculture. *Proceedings of the National Academy of Sciences of the United States of America*, *108*(50), 20260–20264.

Torruco-Uco, J., Chel-Guerrero, L., Martínez-Ayala, A., Dávila-Ortíz, G., & Betancur-Ancona, D. (2009). Angiotensin-I converting enzyme inhibitory and antioxidant activities of protein hydrolysates from *Phaseolus lunatus* and *Phaseolus vulgaris* seeds. *LWT-Food Science and Technology*, *42*(10), 1597–1604.

Tsumura, K., Saito, T., Tsuge, K., Ashida, H., Kugimiya, W., & Inouye, K. (2005). Functional properties of soy protein hydrolysates obtained by selective proteolysis. *LWT-Food Science and Technology*, *38*(3), 255–261.

Turner, A. J., & Hooper, N. M. (2002). The angiotensin-converting enzyme gene family: Genomics and pharmacology. *Trends in Pharmacological Sciences, 23*(4), 177–183.

Udenigwe, C. C. & Aluko, R. E. (2012). Food protein-derived bioactive peptides: Production, processing, and potential health benefits. *Journal of Food Science*, *77*(1), R11–R24.

Wahab, A. G. (2016). *Malaysia oilseeds and products annual 2016*. Retrieved from https://www.fas.usda.gov/data/malaysia-oilseeds-and-products-annual-0

Wan Mohtar, W. A. A. Q. I., Hamid, A. A., Abd-Aziz, S., Muhamad, S. K. S., & Saari, N. (2014). Preparation of bioactive peptides with high angiotensin converting enzyme inhibitory activity from winged bean [*Psophocarpus tetragonolobus* (L.) DC.] seed. *Journal of Food Science Technology*, *51*(12), 3658–3668.

Wang, C., Wang, Q., & Tian, J. (2010). Optimization of enzymatic production of oligopeptides from apricot almonds meal with neutrase and N120P. *International Journal of Molecular Sciences*, *11*(12), 4952–4961.

Wang, R., Zhao, Y., He, X., Ma, X., Yan, X., Sun, Y., . . . He, J. (2009). Impact of hypertension on health-related quality of life in a population-based study in Shanghai, China. *Public Health*, *123*(8), 534–539.

Wood, R. (1995). Bronchospasm and cough as adverse reactions to the ACE inhibitors captopril, enalapril and lisinopril. A controlled retrospective cohort study. *British Journal of Clinical Pharmacology*, *39*(3), 265–270.

World Health Organization. (2014). *Global status report on noncommunicable diseases 2014*. Geneva, Switzerland: Author.

Wu, G., Fanzo, J., Miller, D. D., Pingali, P., Post, M., Steiner, J. L., & Thalacker-Mercer, A. E. (2014). Production and supply of high-quality food protein for human consumption: Sustainability, challenges, and innovations. *Annals of the New York Academy of Sciences*, *1321*(1), 1–19.

Wu, J., Aluko, R. E., & Muir, A. D. (2002). Improved method for direct high-performance liquid chromatography assay of angiotensin-converting enzyme-catalyzed reactions. *Journal of Chromatography A*, *950*(1–2), 125–130.

Wu, J. & Ding, X. (2001). Hypotensive and physiological effect of angiotensin converting enzyme inhibitory peptides derived from soy protein on spontaneously hypertensive rats. *Journal of Agricultural and Food Chemistry*, *49*(1), 501–506.

Wu, J. & Ding, X. (2002). Characterization of inhibition and stability of soy protein-derived angiotensin I-converting enzyme inhibitory peptides. *Food Research International*, *35*(4), 367–375.

Wu, J., Aluko, R. E., & Nakai, S. (2006a). Structural requirements of angiotensin I-converting enzyme inhibitory peptides: Quantitative structure-activity relationship study of di- and tripeptides. *Journal of Agricultural and Food Chemistry*, *54*(3), 732–738.

Wu, J., Aluko, R. E., & Nakai, S. (2006b). Structural requirements of angiotensin I-converting enzyme inhibitory peptides: Quantitative structure-activity relationship modeling of peptides containing 4-10 amino acid residues. *QSAR & Combinatorial Science*, *25*(10), 873–880.

Yanagisawa, Y., Akazawa, T., Abe, T., & Sasahara, T. (1997). Changes in free amino acid and Kjeldahl N concentrations in seeds from vegetable-type and grain-type soybean cultivars during the cropping season. *Journal of Agricultural and Food Chemistry*, *45*(5), 1720–1724.

Yang, Y., Marczak, E. D., Yokoo, M., Usui, H., & Yoshikawa, M. (2003). Isolation and antihypertensive effect of angiotensin I-converting enzyme (ACE) inhibitory peptides from spinach rubisco. *Journal of Agricultural and Food Chemistry*, *51*(17), 4897–4902.

Yang, Y., Tao, G., Liu, P., & Liu, J. (2007). Peptide with angiotensin I-converting enzyme inhibitory activity from hydrolysed corn gluten meal. *Journal of Agricultural and Food Chemistry*, *55*(19), 7891–7895.

Yea, C. S., Ebrahimpour, A., Hamid, A. A., Bakar, J., Muhammad, K., & Saari, N. (2014). Winged bean [*Psophorcarpus tetragonolobus* (L.) DC] seeds as an underutilised plant source of bifunctional proteolysate and biopeptides. *Food and Function*, *5*(5), 1007–1016.

Yust, M. M., Pedroche, J., Girón-Calle, J., Alaiz, M., Millán, F., & Vioque, J. (2003). Production of ace inhibitory peptides by digestion of chickpea legumin with alcalase. *Food Chemistry*, *81*(3), 363–369.

Zarei, M., Ebrahimpour, A., Abdul-Hamid, A., Anwar, F., Bakar, F. A., Philip, R., & Saari, N. (2014). Identification and characterization of papain-generated antioxidant peptides from palm kernel cake proteins. *Food Research International*, *62*, 726–734.

Zarkadas, C. G., Gagnon, C., Gleddie, S., Khanizadeh, S., Cober, E. R., & Guillemette, R. J. D. (2007). Assessment of the protein quality of fourteen soybean [*Glycine max* (L.) Merr.] cultivars using amino acid analysis and two-dimensional electrophoresis. *Food Research International*, *40*(1), 129–146.

Zhang, L. & Kyei-Boahen, S. (2007). Growth and yield of vegetable soybean (Edamame) in Mississippi. *HortTechnology*, *17*(1), 26–31.