EVALUATION OF BIOACTIVE PEPTIDES FROM KENAF (*Hibiscus cannabinus* L.) SEED PROTEIN FOR ANGIOTENSIN-CONVERTING ENZYME INHIBITORY ACTIVITY

By

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The aim of this study was to produce bioactive peptides synthesized from kenaf (*Hibiscus cannabinus* L.) seed, which is a byproduct of the kenaf industry and investigate on its antihypertensive activity. Kenaf seed was observed to produce 12.2 % yield, with 70.2 % protein content. Papain-generated hydrolysates was observed to produce a very high angiotensin-converting enzyme (ACE) inhibitory activity, with 95.47 %. Therefore, it was decided that papain-generated hydrolysates to be further studied. Optimum condition of 65 °C, pH 6.5, 2.25 hours and E/S ratio 0.03 was determined and produced a maximum degree of hydrolysis (DH) of 58.98 % and 78.45 % ACE inhibitory activity. It was observed that the solubility, foaming and emulsification activity was low at pH 4 and increased up to pH 9 and the water and oil absorption capacity was observed to be lower in kenaf seed protein hydrolysate (KSPH) as compared to kenaf seed protein isolate (KSPI). The *in vivo* biological activity of KSPH was observed to be the most optimum dosage at 300 mg/kg. Profiling of the peptides showed that peptides with molecular weight 2 to 5 kDa exerted the highest ACE inhibitory (82.27 %) with hydrophobic peptides in the later-eluting fractions. Sequencing showed that peptides INPPSTTN, AKSCVVFP, LLLHAL, WTIPTPS, ALFYWVS and LYWSYLYN possessed high ACE inhibitory activities. Molecular docking reflected that peptide LYWSYLYN with the lowest Glidescore value (-14.66 kJ/mol) possessed the strongest binding affinity towards the ACE protein and kinetic studies discovered that peptide LYWSYLYN which underwent competitive inhibition displayed the lowest Ki value (0.017 mM) which was indicated the most effective ACE inhibitor amongst the other peptides. Thus, it can be concluded that bioactive peptides derived from kenaf seed protein has high ACE inhibitory activity which is a potential functional food ingredient for development of various food applications.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk Ijazah Doktor Falsafah

PENILAIAN PEPTIDA BIOAKTIF MELALUI PROTEIN DARIPADA BIJI KENAF (*Hibiscus cannabinus* L.) BAGI AKTIVITI RENCATAN ENZIM PENUKARAN ANGIOTENSIN

Oleh

NURUL DHANIA ZAHARUDDIN

November 2022

Pengerusi: Profesor Nazamid Saari, PhD
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Hala tuju kajian ini adalah untuk menghasilkan peptida bioaktif yang disentisis daripada biji kenaf (*Hibiscus cannabinus* L.) yang merupakan bahan buangan dalam industri kenaf dan mengkaji aktiviti hipertensi protin tersebut. Protin daripada biji kenaf telah dipencilkan dan memproduksikan 12.2 % hasil protin dan kandungan protin sebanyak 70.2 %. Hydrolisat yang dijana oleh enzim papain telah menghasilkan aktiviti rencatan angiotensin (ACE) yang sangat tinggi, iaitu 95.47 % dan telah dipilih untuk dikaji dengan lebih mendalam. Kondisi yang optima iaitu 65 °C, pH 6.5, 2.25 jam dan nisbah E/S sebanyak 0.03 telah dikenalpasti dan telah menghasilkan darjah hidrolisa (DH) sebanyak 58.98 % dan activiti rencatan ACE sebanyak 78.45 %. Ia diperhatikan bahawa aktiviti keterlarutan, pembuihan dan pengemulsian adalah rendah pada pH 4 dan tinggi pada pH 9 dan penyerapan air dan minyak diperhatikan adalah rendah pada protin hidrolisat biji kenaf (PHBK) berbanding dengan protin isolate biji kenaf (PIBK). Aktiviti biologi *in vivo* telah diperhatikan paling optima pada dos 300 mg/kg. Pemprofilan peptida menunjukkan bahawa peptida dengan berat molekul 2 hingga 5 kDa menunjukkan aktiviti rencatan ACE yang paling tinggi (82.27 %) dengan sifat hidrofobik pada sampel yang ditapis kemudian. Proses pensekuenan menunjukkan bahawa peptida-peptida INPPSTTN, AKSCVVFP, LLLHAL, WTIPTPS, ALFYWVS dan LYWSYLYN mengandungi aktiviti rencatan ACE yang tinggi. Kaedah penyambungan molekul pula menggambarkan bahawa peptida LYWSYLYN yang menghasilkan bacaan skor peluncuran yang terendah (-14.66 kJ/mol) menghasilkan tahap pengikatan yang paling tinggi terhadap protin ACE dan kajian kinetik membuktikan bahawa peptida LYWSYLYN menjalani aktiviti rencatan kompetetif dengan nilai Ki yang terendah (0.017 mM). Ini menunjukkan bahawa ianya adalah peptida rencatan yang paling efektif berbanding peptida-peptida yang lain. Oleh itu, ia boleh disimpulkan bahawa peptida bioaktif yang dihasilkan daripada protin yang diperoleh dari biji kenaf mempunyai aktiviti rencatan ACE yang tinggi dan adalah berpotensi untuk digunakan sebagai bahan aktif di dalam pelbagai jenis makanan berfungsi.

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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 Doctor of Philosophy. The members of the Supervisory Committee were as follows:

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LIST OF ABBREVIATIONS

KSPH	Kenaf seed protein hydrolysate
KSPI	Kenaf seed protein isolate
RSM	Response surface methodology
SHR	Spontaneously hypertensive rats
BP	Blood pressure
RP-HPLC	Reverse phase-high performance liquid chromatography
QTOF-LC/MS	Quadrupole time of flight-liquid chromatography/mass spectrometer
ACE	Angiotensin-converting enzyme
DPPH	2,2-Diphenyl-1-picrylhydrazyl
DPP-IV	Dipeptidyl peptidase IV
DH	Degree of hydrolysis
CVD	Cardiovascular disease
ROS	Reactive oxygen species
FRAP	Ferric reducing antioxidant power
DM	Diabetes mellitus
GLP	Glucagon-like peptide
OPA	O-phthaldialdehyde
TPTZ	2,4,6-Tris(2-pyridyl)-s-triazine
PITC	Phenylisothiocyanate
BSC	Benzenesulphonyl chloride
MWCO	Molecular weight cut off
TFA	Trifluoroacetic acid
HHL	Hippuryl-L-histidyl-L-leucine
EAA	Essential amino acids

ANOVA	Analysis of variance
WAC	Water absorption capacity
OAC	Oil absorption capacity
ACN	Acetonitrile

CHAPTER 1

INTRODUCTION

The kenaf (*Hibiscus cannabinus* L.) plant is a vast producing crop and is suitably grown in the tropical climate. Therefore, it has been abundantly grown in Malaysia, due to the weather and soil suitability, up to a point where it was suggested to replace the extensive tobacco plantation. Kenaf plant is able to produce quite a voluminous number of seeds, within the vicinity of 36,000 to 40,000 seeds/kg. The statistic of kenaf seed production in Malaysia is an annual increase from 7190 kg of kenaf seeds in 2006 to 151,250 kg in 2011 (Chew et al. 2017). In the past, kenaf stalk was widely used to produce fiber for the production of sacs, canvases, ropes and carpet while the oil from kenaf seed was used to act as antioxidant, anticholesterol and also against certain type of diseases such as cancer. However, the usage of kenaf seed protein has not been widely explored yet. Due to this, this research is aimed to exploit the use of kenaf seed protein since it contains quite a high content in kenaf seeds. The kenaf seed protein was isolated to produce the maximum yield to be studied and investigated. Furthermore, due to its vast production, kenaf seed has always been rendered as agricultural waste. Therefore, it gives the more reason to discover the usage of kenaf seed protein to combat against the high rising number of non-communicable disesases (NCD) worldwide. In the past, a few researches have been done on kenaf seed protein, although not many, which were investigated by Mariod et al. (2010) who studied the functional properties of kenaf seed protein concentrates. Arulrajah et al. (2020) on the other hand discovered on the antibacterial activity of kenaf seed bioactive peptides and Ibrahim et al. (2020) studied on the application of kenaf seed in the production of kenaf-based tofu. However, none of the works have focused on the multifunctional and antihypertensive activity of the peptides.

Protein isolate yield is the amount of protein derived from isolation of protein from the kenaf seed and protein content is the amount of protein present in the kenaf seed. Protein hydrolysates on the other hand are the protein that is obtained after the process of hydrolysis, which is the cutting of protein by the enzymes. The protein isolate yield from kenaf seed was observed to be higher than past studies, therefore, it is of high interest to explore more on its potential in the application against NCDs that is highly increasing worldwide. Bioactive peptides are segments derived from protein through a process called hydrolysis. They possess bioactive properties that have proven to be effective as health-promoting agents to combat many types of diseases, mainly cardiovascular disease, inflammation and metabolic diseases (Udenigwe and Aluko, 2012). In recent years, various investigations have been invested into the production, characterization and applications of bioactive peptides to explore more on their diverse health benefits. Enzymatic hydrolysis is the most specific, easily handled and safest way to produce bioactive peptides. It uses plant or animal derived enzymes and is executed in a controlled environment at a suitable temperature and pH. It is highly specific as different enzymes are able to cut through the protein at different sites, producing specific types of peptides and amino acids.

Therefore, enzymatic hydrolysis is able to produce the desired peptides that are needed to produce a specific type of bioactive agent. Peptides produced by hydrolysis consist of smaller molecular size and less compact structure as compared to native proteins. These peptides may enhance the functional properties derived from the original proteins (Barac et al., 2006). Numerous researches have been done on both animal and plant based protein, such as from sea cucumber (Ghanbari et al., 2015), beef myofibrillar protein (Lee and Hur, 2019), stone fish (Auwal et al., 2017), milk (Otte et al., 2007), soybean (Gouda et al., 2006), horse gram flour (Bhaskar et al., 2019) and palm kernel cake (Zarei et al., 2015). Many studies have also been conducted on seeds such as pea seeds (Barac et al., 2006), quinoa seeds (Aluko and Monu, 2003), goat seeds (Mirdhayati et al., 2015) and tomato seeds (Zhang et al., 2015) but limited studies have been done on kenaf seeds. Identification of peptides enables the investigation of amino acids in the peptides that are responsible for the antihypertensive activity. It is also able to identify the molecular dinamics of the peptides towards the enzyme protein as well as the effectiveness of the peptides as inhibitors. Therefore, the identification and characterization of peptides is useful in its investigation as bioactive inhibitors of NCDs.

The NCDs that are studied in this research are hypertension, oxidative stress and diabetics. Hypertension is a common chronic cardiovascular disease. Blood pressure occurs at systolic blood pressure of more than 140 mmHg and diastolic blood pressure above 90 mmHg. It is estimated that 1.13 billion people worldwide have hypertension, and affects up to 30 % of the adult population in most countries. Angiotensin-converting enzyme plays a crucial physiological role in moderating blood pressure. ACE causes the conversion of angiotensin I to a vasoconstrictor, angiotensin II, while inactivating the vasodilator, bradykinin. (Li et al., 2005). Therefore, the inhibition of ACE is important for management of this disease. Oxidative stress occurs from an excess of reactive oxygen species (ROS) that may cause oxidative damage to cells and tissues in the body. It can then lead to the occurrence of cardiovascular diseases, stroke or even cancer. Thus, antioxidative agents may stabilize the oxidative chain reaction and reduce the amount of ROS in the body, protecting the cells and tissues in the body from lipid oxidation. Diabetes mellitus is one type of chronic disease that is highly increasing worldwide. It occurs from the depletion of glucagon-like peptide-1 (GLP-1) that is responsible to regulate the production of insulin. Dipeptidyl-peptidase-IV is a protease enzyme that exist in the body and is able to inactivate GLP-1. Therefore, inhibition of DPP-IV may reduce the metabolism of GLP-1 and increase insulin secretion. The commercial synthetic drug that is commonly administered to cure these NCDs may cause certain side effects. Since kenaf seed contains quite a high amount of protein and its potential as bioactive peptides have not been explored, it is of high value to investigate more on its usage to act against the high rising number of NCDs.

Thus, this research was conducted based on the following objectives:

General objective: To evaluate the bioactive peptides synthesized from kenaf (*Hibiscus cannabinus* L.) seed protein for its ACE-inhibitory activity.

Specific objective:

1. To hydrolyse protein from kenaf seed using enzymatic hydrolysis and evaluate on three types of non-communicable diseases which are ACE inhibitory, antioxidant and antidiabetic activity

2. To optimize the hydrolysis conditions for the production of KSPH and its ACE inhibitory activity using response surface methodology and observe on the physical characteristics such as solubility, foaming, emulsification, water and oil absorption capacity

3. To profile KSPH to its molecular size using ultrafiltration and hydrophobicity using RP-HPLC and investigate on the *in vivo* efficacy of KSPH on SHR.

4. To identify the peptides by sequencing, study on the binding affinities of the peptides by molecular docking and investigate on the efficacy of the peptides towards ACE inhibition using kinetic studies.

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