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To cite this article: Sima Maleki & Seyed Hadi Razavi (2020): Pulses' germination and fermentation: Two bioprocessing against hypertension by releasing ACE inhibitory peptides, Critical Reviews in Food Science and Nutrition, DOI: [10.1080/10408398.2020.1789551](https://doi.org/10.1080/10408398.2020.1789551)

To link to this article: <https://doi.org/10.1080/10408398.2020.1789551>



Published online: 14 Jul 2020.



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REVIEW



## Pulses' germination and fermentation: Two bioprocessing against hypertension by releasing ACE inhibitory peptides

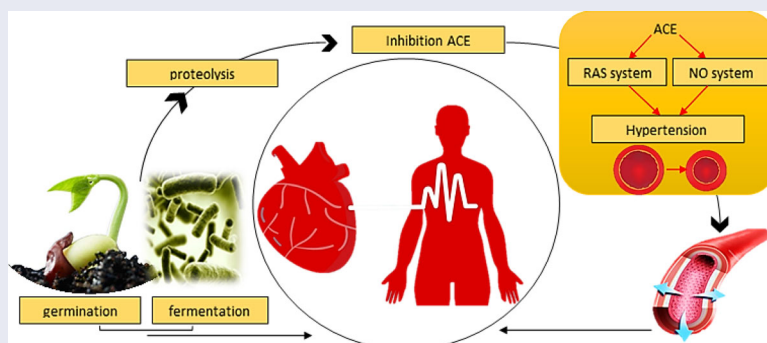
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### ABSTRACT

Angiotensin-Converting Enzyme (ACE) is one of the main blood pressure regulators in the renin-angiotensin system leading to hypertension. Hypertension is known as the modern world disease which increases the risk of serious human health problems. Synthetic drugs and some natural compounds could treat this disease by binding to ACE and reducing its activity. Pulses, one of the legumes group, that are the rich in protein sources in the human diet, have several bioactive compounds with ACE inhibitory (ACE I) properties. However, several processes need to break down proteins and improve ACE I activity in foods. Germination and fermentation, known by bioprocessing, could make releasing bioactive peptides and polyphenols and exhibit ACE I and either other health properties such as antimicrobial, antioxidant, anti-diabetic and anticancer activities. Various factors such as kind of selective culture, temperature, time and humidity affect these processes. This review summarizes relevant studies about the effect of pulses' germination and fermentation to produce ACE I activity compounds and also explains about main parameters affecting the health properties of these two bioprocessing to treat hypertension that could lead to the development of their application in pharmaceuticals instead of synthetic drugs.

### GRAPHICAL ABSTRACT



### KEYWORDS

Bioactive compounds; ACE; ACE I; functional foods; pulses; fermentation; germination

### Introduction

Hypertension (high blood pressure) is a physiological condition characterized by persistent overwhelming blood pressure in the arteries (elevated to at least 140 mm Hg systolic or 90 mmHg diastolic consistently) which cause some major risk e.g. stroke, heart attack and other cardiovascular diseases (Huang, Davidge, and Wu 2013; Teneva et al. 2018). There are several biological pathways to regulate blood pressure in living organisms (Ma, Boye, and Hu 2018). Two and main pathways in the human body are known by kinin–nitric oxide and the renin-angiotensin-aldosterone systems (RAAS) (Chel-Guerrero et al. 2012; Bhatnagar et al. 2018). In the kinin–nitric oxide (NO) system, the accumulation of

intracellular  $\text{Ca}^{+2}$  ions by bradykinin could active nitric oxide synthases (NOSs). NOSs generate nitric oxide which makes a powerful vasodilator effect and decreases hypertension (Piovesana et al. 2018). In RAAS, renin (a kind of hormone that is secreted by the kidneys) converts angiotensinogen to the pre-hypertensive angiotensin I (DRVYIHPFHL sequence). In continue, angiotensin II (DRVYIHPF sequence), an active form of the hormone, is produced by angiotensin-converting enzyme (ACE), a carboxyl and zinc metallopeptidase enzyme, via removing two amine acid (His-Leu) from the C-terminus part of angiotensin I (a kind of hormone). This hormone raises blood pressure by a direct effect on the blood vessels (Martin and Deussen 2017; Bhatnagar et al. 2018). ACE also degrades

Bradykinin which is an inflammatory mediator affecting the release of aldosterone in the adrenal cortex (Puchalska, Marina Alegre, and García López 2015; Teneva et al. 2018). As a result, the excessive action of ACE makes hypertension (Jayathilake et al. 2018; Teneva et al. 2018) and its inhibiting could be one solution to cure this diseases (Piovesana et al. 2018; Bhatnagar et al. 2018). There are several drugs e.g. benazepril, captopril, and enalapril to control the ACE activity (Hanafi et al. 2018; Piovesana et al. 2018). Except for drugs' high cost, they often cause bad side-effects such as dry cough, angioedema, allergic reactions, taste disturbances, and skin rashes (Hanafi et al. 2018; Orano-Tamayo, Valverde, and Paredes-López 2019). These two reasons encourage people to consume functional and nutrient-fortified foods with ACE inhibitory (ACE I) potency compounds (Hanafi et al. 2018).

Natural ACE inhibitors such as food-derived peptides and phenolic ingredients are either safe and low-cost compounds with several health effects e.g. anticancer, immunomodulatory, analgesic, antimicrobial, antioxidants and anti-thrombosis that also are known by bioactive components (Leblanc, Luerce, and Miyoshi 2018; Orano-Tamayo, Valverde, and Paredes-López 2019). Bioactive peptides (BPs) are usually constituted of 2–20 amino acids and the most remarkable subovergroup to inhibit ACE I (Orona-Sanlier, Gökçen, and Sezgin 2017; Orano-Tamayo, Valverde, and Paredes-López 2019; Piovesana et al. 2018). The two main factors affect the potential of ACE inhibitory activity are the weight and the sequences of cleaved peptides by proteolysis (Garcia-Mora et al. 2014; Nawaz et al. 2017; Bautista-Expósito et al. 2018).

Several rich-in-protein natural sources such as, milk, cheese, meat, chicken, egg, fish and legumes (Orano-Tamayo, Valverde, and Paredes-López 2019), and some other foods e.g. fruits, vegetables, tea, wine, and mushrooms (Huang, Davidge, and Wu 2013) have ACE I activity and antihypertensive effects (Huang, Davidge, and Wu 2013; Orona-Tamayo et al. 2019). Leguminosae family (or Fabaceae), the second most consumable source of the human diet after cereals, is the high in nutritional protein (18–32%), and polyphenolic components that not only reduce cardiovascular disease risk factors, but also could effect on diabetes, cancer, and body weight (González-Múniz, Martín-Martínez, and Bonache 2016; Mamilla and Mishra 2017; Jayathilake et al. 2018; Qamar et al. 2019; Gobetti et al. 2019; Bessada, Barreira, and Oliveira 2019). Pulses are belonging to the legume family and divided to dry beans, dry broad beans, dry peas, chickpeas, dry cowpea, pigeon pea, lentil, groundnut, vetches, and lupin, according to Food and Agriculture Organization (FAO). As same as other legumes, they have high protein levels, carbohydrate-rich endosperm, and bioactive compounds (Duranti 2006; Rao et al. 2018). The pulses characteristics and their health benefits have been shown in Table 1. Good balance of pulses amino acids (De Souza Rocha et al. 2015; Toledo et al. 2016; Xiao et al. 2018), not allergenic protein in pea (Roy, Boye, and Simpson 2010; Burger and Zhang 2019; Venkidasamy et al. 2019), high resisting protein agent cooking (86.9%

total protein) in chickpea (Roy, Boye, and Simpson 2010; Ribeiro et al. 2017; Qamar et al. 2019), low levels of anti-nutritional factors affecting the digestibility of nutrients in cowpea (Duññas et al. 2005; Joung Ha et al. 2010; Kapravelou et al. 2014; Hachibamba et al. 2013) and chickpea (Yust et al. 2003; Ribeiro et al. 2017) and the ability to modulate intestinal microflora in chickpea (Yust et al. 2003; Ribeiro et al. 2017) could make pulses a good alternative for hypertension drugs (Mora-Escobedo, Berrios, and Lopez 2014; López-Barrios et al. 2018; Jayathilake et al. 2018). Pulses' bioactive peptides with valuable nutritional properties are inactive in the intact protein and activated as soon as cleaved by enzymes during food processing and bioprocessing (Daliri, Lee, and Oh 2017; Qamar et al. 2019).

Legumes/pulses' bioprocessing includes enzymatic hydrolysis, germination and fermentation which degrade legumes protein and releases smaller peptide fragments and amino acids consequently affecting their biological activity and ACE I activity (González-Múniz, Martín-Martínez, and Bonache 2016; Xiao et al. 2018; Leblanc, Luerce, and Miyoshi 2018). Enzymatic hydrolysis by gastrointestinal enzymes (pepsin and a-chymotrypsin) is one of the most important seeds bioprocessing (Campos and Guerrero 2010; Garcia-Mora et al. 2014; Garcia-Mora, Frias, et al. 2015; González-Múniz, Martín-Martínez, and Bonache 2016; Xiao et al. 2018). Fermentation is also another important food bioprocessing that its potency to moderate hypertension has been recently recorded (Sanjukta and Rai 2016; Sanlier, Gökçen, and Sezgin 2017). Based on studies, germination of grains is the last seeds bioprocessing that may enhance the content of ACE I potency compounds by activation endogenous enzyme (Sanjukta and Rai 2016; Saleh et al. 2018). Figure 1 shows pulses' bioprocessing and all related parameters to germination and fermentation which affect the ACE I activity of grains.

This review focuses on the potential of the most popular pulses, beans, lentil, and pea, to produce the ACE I peptides via germination and fermentation. As a matter of fact, these two bioprocessing are economical technology to produce bioactive peptides that could apply together as a complementary process. The role of kind of seeds, proteolysis, weight, sequences of peptides and environment condition parameters to produce bioactive peptides with ACE I activity would be discussed, too.

### **Legumes/pulses processing/bioprocessing to enhance ACE I compounds**

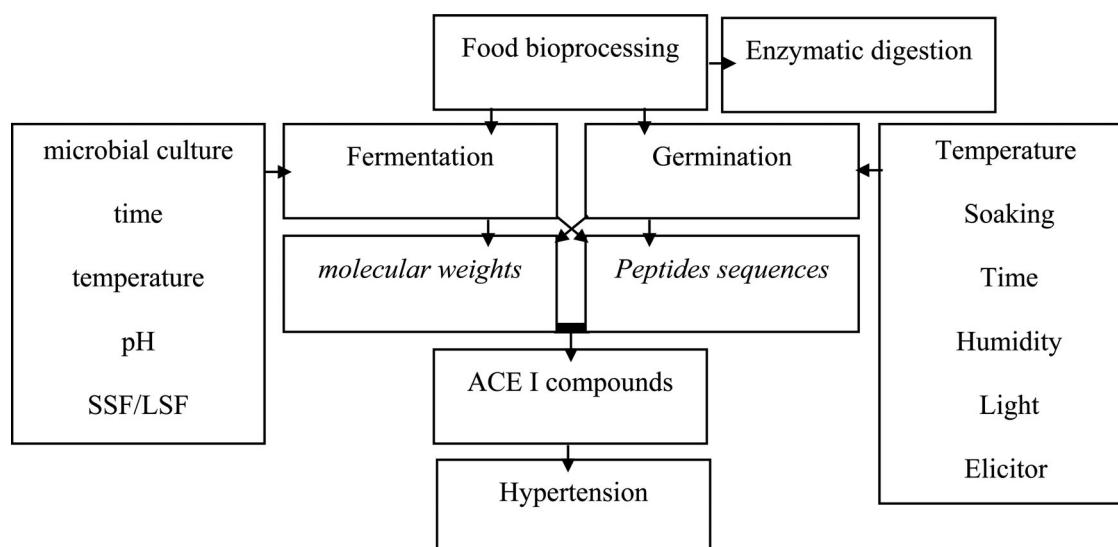
Legumes/Pulses processing e.g. enzymatic proteolysis, hydrostatic pressure (HP) (Garcia-Mora, Frias, et al. 2015), gastrointestinal digestion (Bautista-Expósito et al. 2018), soaking, germination process (Karakaya et al. 2016), fermentation (Torino et al. 2013) and heat treatment could separately or together generate a significant amount of bio-accessible peptides and phenolic compounds (Awika and Duodu 2016; Khosravi, Razavi, and Fadda 2020). For instance, the results indicated that thermal, ultrasonic processing, cooking, enzyme digestion of cooked cowpeas and protein hydrolysis

**Table 1.** Pulses characteristics, their health effect and health components.

Pulses	Average of components	Health effect	Healthy compounds	ref
Beans	Protein: 21–25% Carbohydrate: 60–65% Fiber: 3–7% Fat: 0.8–1.5% (1)	antimicrobial, antioxidant, antithrombotic, and antihypertensive (3) inhibited lipid accumulation in adipocytes and contributed to the control of glucose absorption by stimulating insulin secretion by pancreatic cells (4) inhibition $\alpha$ -amylase activity and controlling or minimize type-2 diabetes (5) inhibition DPP-IV (IC <sub>50</sub> 0.1 to 1.0 mg of protein/mL) (6)	biological compounds and bean's peptides (4) (5)	1- Dueñas et al. (2015); Harnedy et al. (2015) 2- Lee et al. (2018); Bessada et al. (2019) 3- Durak et al. (2013); Mojica et al. (2014); Toledo et al. (2016); Los et al. (2018) 4- Toledo et al. (2016) 5- De souza Rocha et al. (2015) 6- Mojica et al. (2014)
Lentil ( <i>Lens culinaris</i> Medik.) known as red dahl, masur, massar, masuri tillseed and split pea (1)	Protein: 20–31.7% Carbohydrate: 63% Fiber: 20.44% Fat: 1% (mainly oleic, linoleic and palmitic acid) (2) (3)	oxidative stress defense, inhibit the expression of pro-inflammatory molecules, decrease cholesterol, lipid, cardiovascular disease, cancer/colon cancer, atherosclerosis, diabetes, and immune deficiency diseases (4)	phytochemical composition such as phenolic compounds: proanthocyanidins, flavones, flavonols, stilbenes, phenolic acids, tannins, catechin, and anthocyanidins (3) (4)	1- Roy et al. (2010); Garcia-Mora et al. (2014); Aslani et al. (2015); Bautista-Expósito et al. (2018) 2- Gómez-Favela et al. (2017) 3- Faris Takruri and Issa, (2013); Garcia-Mora et al. (2014); Aslani et al. (2015); Peñas et al. (2015); Jarpa-Parra (2017); Bautista-Expósito et al. (2018) 4- Roy et al. (2010); Aslani et al. (2015); Lopes et al. (2016); Bautista-Expósito et al. (2018); Zhang et al. (2018)
Pea ( <i>Pisum sativum</i> L.) (1)	Protein: 20–30%, Carbohydrate: 3–10% Fiber: 22.03% Lipid: 0.5–3.5% (2)(3)	antioxidant activity, ACE I activity and decrease the incidence of colon cancer, type-2 diabetes, decrease LDL-cholesterol and heart disease (4)	bioactive peptides phenolic compounds, fiber (soluble and insoluble), complex carbohydrates, vitamins (4) not allergenic protein (5)	1- Aluko (2015); Burger and Zhang, (2019) 2- Gómez-Favela et al. (2017) 3- Burger and Zhang, (2019) 4- Jin et al. (2012); Aluko, (2015); Ma (2018); Burger and Zhang (2019) 5- Roy et al. (2010); Venkidasamy et al. (2019)
Chickpea ( <i>Cicer arietinum</i> L.)(1)	Protein: 18%– 24% Carbohydrate: 60%–70% Fiber: 13.9% Fat: 3% (2)(3)	prevent chronic diseases e.g. cardiovascular, diabetes, osteoporosis, and hypertension), reduce the LDL cholesterol and cancer (1)	essential amino acids and protein, unsaturated fatty acids (1)(4)	1- Roy et al. (2010); Ribeiro et al. (2017); Bessada et al. (2019) 2- Sofi, Singh, Chhikara, and Panghal (2020) 983- Gómez-Favela et al. (2017) 4- Venkidasamy et al. (2019)
Cow pea ( <i>Vigna unguiculata</i> ) known as dongbu, black-eyed pea, southern pea, and crowder (1)	Protein: 23–32% Carbohydrate: 60% Fiber: 2.5% to 32% Fat: 1% (1)	antioxidant, anti-atherogenic, anti-cancer properties (2), anti-diabetic and anti-inflammatory effects (3), limit the presence of anti-nutritional factors affecting the digestibility of nutrients (4), moderate hypercholesterolemia and significantly reduced total cholesterol (12 %) (6)	synergistic relationship between cowpea peptides and polyphenols (2) e.g. phenolic acids derivatives, flavonol glycosides, the unusual Proanthocyanid (PA), and/or flavan-3-ols (5) vitamins (5) and protein (6)	1- Joung Ha et al. (2010); Segura-Campos et al. (2011); Awika and Duodu, (2016); Jayathilake et al. (2018) 2- Jin et al. (2012); Awika and Duodu (2016) 3- Ojwang et al. (2015); Awika and Duodu (2016) 4- Dueñas et al. (2005); Joung (2010); Hachibamba et al. (2013); Kapravelou et al. (2014) 5- Hachibamba et al. (2013); Kapravelou et al. (2014); Jayathilake et al. (2018) 6- Frota, Santos, et al. (2015)

could inhibit human LDL oxidation (Hachibamba et al. 2013) and increase the radical scavenging (Quansah et al. 2013) and ACE I activity (ACE I% 97.19%) (Drago et al. 2016). In another study, González-Múniz, Martín-Martínez, and Bonache (2016) demonstrated that both antioxidant and ACE I activity (IC<sub>50</sub> = 44–120  $\mu$ M) increased by producing a certain type of peptides during gastrointestinal digestion of

lentil proteins (LP). Hydrolyzed- proteins of cowpea flour for manufacturing pasta (5–10% flour) and bread (1 or 3%) (Drago et al. 2016; Franco-Miranda et al. 2017) and Hydrolyzed- proteins of lentil (Garcia-Mora et al. 2014) exhibited a high amount of thermal stable active compounds with ACE I potency and ACE I activity (IC<sub>50</sub> 0.14 mg of protein/mL), respectively. Based on studies, germination and



**Figure 1.** Pulses' bioprocessing and all related parameters to germination and fermentation which affect the ACE I activity of grains.

**Table 2.** Chemical composition (%) of different variety of raw bean.

Beans variety	Proteins%	Carbohydrates%	fats%	References
Dark bean	17.7	77.4	1.1	Geil and Anderson (2014)
Common black beans ( <i>Rhynchosia nulubilis</i> )	23	70.3	2.7	Xiao et al. (2018) (Lee et al. 2018)
Common beans ( <i>Phaseolus vulgaris</i> L.)	24	61.3	1.6	Xiao et al. (2018) Garcia-Mora et al. (2015)
Kidney beans	27	2 (crude fiber)	1.9	Wani, et al. (2013); Xiao et al. (2018)
Adzuki bean	25	65.4	0.45	Durak et al. (2013), Valdez-Ortiz, (2012)
Lima beans ( <i>Phaseolus lunatus</i> )	210–260 g/kg	550–640 g/kg	10–23 g/kg	Chel-Guerrero et al. (2012)

fermentation are two welcome and low-cost legumes/pulses' bioprocessing to enrich pulses' ACE I activity, provide health beneficial effect by releasing bioactive components and reduce anti-nutritional factors (Bartolome, Estrella, and Hernandez 1997; Mora-Escobedo, Berrios, and Lopez 2014; Karakaya et al. 2016; Leblanc, Luerce, and Miyoshi 2018; Wu and Xu 2019).

However, sometimes these processes have negative effects on ACE I and high ACE inhibition is only found in crude extracts of seed (Garcia-Mora, Frias, et al. 2015; Zhang, Peng, et al. 2018). Zhang, Peng, et al. (2018) demonstrated the  $IC_{50}$  value reduced 50% in ACE I potency after cooking as same as purification and fractionating of crude phenolic extracts. Garcia-Mora, Frias, et al. (2015) reported that in vitro gastrointestinal digestion caused a slight loss of ACE I activity by higher  $IC_{50}$  values 0.27 mg peptide/mL in compared to non-digested control ( $IC_{50}$  0.20 mg peptide/mL).

The health benefits of bioactive peptides affected the ACE I activity depend on some factors such as the protein content (kind of pulses), the Proteolysis, weight and sequences of peptides released during bioprocessing, different cultivars, and processing methods that was discussed in the following part of article (De Souza Rocha et al. 2015; Rudolph et al. 2017; Los et al. 2018; Zhang, Peng, et al. 2018; Manzanares et al. 2019; Qamar et al. 2019).

### Main parameters affecting ACE I compounds potency

#### Kind of pulses

The first factor to determine amount of bioactive peptides releasing during germination and fermentation and affect

the proteolysis, weight and kind of peptides sequencing is the quantity and quality of proteins which is 21–25% in Beans (Dueñas et al. 2015; Harnedy, O'Keeffe, and FitzGerald 2015), lentil 20–31.7% (Aslani et al. 2015; Jarpa-Parra 2017; Bautista-Expósito et al. 2018), 20–30% in pea (Burger and Zhang 2019), 10–15% in Chickpea (Gómez-Favela et al. 2017; Sofi et al. 2020) and 23–32% in cowpeas (Awika and Duodu 2016; Jayatilake et al. 2018). Compared to whole seeds, cowpea have a higher quantity of crude protein (256.0 g/kg), and protein dispersibility (74.5%) (Qamar et al. 2019). However, the amount of main content depends on the pulses' varieties (Valdez-Ortiz et al. 2012; Dueñas et al. 2015; Xiao et al. 2018). The Table 2 shows a different variety of bean with their properties and compare their content to each other.

Protein fractions of pulses are another important factor to determine ACE I potency of pulses and divided into albumin, globulin (Storage proteins), prolamins, and glutenin as same as other seeds (Ma, Boye, and Hu 2018; Xiao et al. 2018). The main part of pulses protein is formed by globulins and albumin which is respectively, 45–70% and 10–30% in common bean (De Souza Rocha et al. 2015; Valenzuela-García et al. 2017; Los et al. 2018), 70% and 16% contain both legumin- and vicilin-like proteins in lentil (Peñas et al. 2015; Jarpa-Parra 2017; Xiao et al. 2018), 65–80% and 10–20% in Pea (Burger and Zhang 2019), legumin made up of six  $\alpha\beta$  subunits with 360 kDa molecular mass in chickpea (Pedroche et al. 2002; Yust et al. 2003) and 44–70% and 20–35% in cowpea (Quansah et al. 2013; De Souza Rocha, Hernandez, and Chang 2014). According to Boye et al. (2010) result, the varieties with higher amounts of legumin



(a globulin and structurally similar to the 11S globulin family) and albumin proteins may have higher bioactive peptides with functional properties such as ACE I (Boye et al. 2010). Boye et al. (2010) suggested the  $IC_{50}$  value of the hydrolyzed red lentil protein and its fractions were 440  $\mu\text{g/mL}$  and 111  $\mu\text{mol/L}$ , respectively, and were different for legumin ( $IC_{50}$  119–440  $\mu\text{g/mL}$ ), albumin ( $IC_{50}$  127  $\mu\text{g/mL}$ ) and vicillin ( $IC_{50}$  135  $\mu\text{g/mL}$ ) fractions.

Well-balanced profile of amino acids especially the essential amino acids e.g. tryptophan, leucine and lysine (Roy, Boye, and Simpson 2010; Joung Ha et al. 2010; Segura-Campos, Chel-Guerre, and Betancur-Ancona 2011; Faris, Takruri, and Issa 2013; Garcia-Mora et al. 2014; Aslani et al. 2015; Awika and Duodu 2016; Jayathilake et al. 2018; Bautista-Expósito et al. 2018; Qamar et al. 2019) and low percentage of sulfuric amino acids (Peñas et al. 2015; Jarpá-Parra 2017; Xiao et al. 2018) also could affect the potential of peptide to ACE I activity. Globulins generally show a higher proportion of serine, aspartic acid, alanine, methionine, valine, lysine and proline and lower glutamine, glycine and cystine content in comparison to albumins (Ghumman et al. 2016; Qamar et al. 2019).

### Proteolysis

The in vitro observational studies indicate that some processes such as soaking, germination, and fermentation could digest protein and increase low-molecular-weight peptides via releasing enzymes (Quansah et al. 2013; Rudolph et al. 2017; Ma, Boye, and Hu 2018). The difference in protein hydrolysis affects the weight of peptides and the potency of the isolated legumes' fraction to inhibit ACE (e.g. ACE I% 87.80–89.16%) and  $IC_{50}$  values (Boye et al. 2010; Hajfathalian et al. 2017). According to Xiao et al. (2018) the protease accessibility to proteins and the number of released essential amino acids/bioactive peptides increased during fermentation (Reyes-Bastidas et al. 2010; Jakubczyk et al. 2017; Xiao et al. 2018). These derived peptides not only could make ACE I activity (Torino et al. 2013) but also inhibit gastrointestinal enzymes e.g.  $\alpha$ -glucosidase and pancreatic lipase in which involved carbohydrate and lipid digestion (González-Múniz, Martín-Martínez, and Bonache 2016). Proteolysis within the gastrointestinal enzymes could decrease or increase ACE I potency by removing amino acid residues. Because the potential ACE I activities of peptides is dependent on amino acid composition and sequence so the gastrointestinal stability is important and bioactive peptides must be stable against gastrointestinal enzymes degradation to reach their target organs and tissues and exert their beneficial effects. However, some times, glucosidase/lipase digestion could randomly help to make the bioactive peptides with anti-hypertension properties (Boye et al. 2010; González-Múniz, Martín-Martínez, and Bonache 2016).

However, sometimes applying fermentation has shown a negative effect on releasing ACE I peptides because of the presence of anti-nutritional factors in pulses and inhibiting protein hydrolysis such as trypsin inhibitors (Suwanmanon and Hsieh 2014; Garcia-Mora et al. 2015; Leblanc, Luerce, and Miyoshi 2018). Suwanmanon and Hsieh (2014) reported

that the greatest antihypertensive effect was observed in the pharmacological treatment (treatment with  $\gamma$ -aminobutyric acid (GABA) and nattokinase) without fermentation. Denaturation and aggregation of protein during processing e.g. steaming before fermentation may also make hard the enzyme accessibility to substrate/protein, so the ACE I activity decreased after this processing (Torino et al. 2013).

### Molecular weights

Molecular weight is one of the main factors to determine the ACE I activity (Campos and Guerrero 2010; Rudolph et al. 2017). Against for large peptide molecules, short-chain amino acid could accumulate with the active site of ACE and inhibit its activity (Garcia-Mora et al. 2014; Nawaz et al. 2017). It was reported that fractions with the lowest molecular weight (<1 kDa) showed the highest ACEI activity, in the contrast to the fraction with the highest molecular weight (>10 kDa) (Campos and Guerrero 2010). Based on a recent study, di- and tripeptides are the most favorable sequences to react to ACE active site (Manzanares et al. 2019). However, several studies demonstrated the high ACE I potency for long sequences of the peptide, too (Aluko et al. 2015; Nawaz et al. 2017).

In fact, the weight of ACE I peptides is correlated to the structure of sequences and the reaction between C-terminal amino acids and activity decrease in longer peptides. However, there are not fully established reason for ACE inhibitory activity for longer peptides yet (Manzanares et al. 2019).

### Peptides sequences

Except for the weight and size of peptides, the sequences of peptides play a predominant role to exhibit antihypertensive activity (Nawaz et al. 2017; Manzanares et al. 2019). Typically, there is a competitive mode between C-terminal tripeptide residues of peptides with ACE I potency for blocking and ACE substrate for binding to the active site of ACE (González-Múniz, Martín-Martínez, and Bonache 2016; Nawaz et al. 2017). According to study, accumulation of hydrophobic, aromatic or branched side chains amino acids e.g. Phe, Pro, Trp, Tyr, Leu, Ile and Val in the C-terminal of tripeptide significantly increase the potent of ACE inhibitory (Garcia-Mora et al. 2014; Rudolph et al. 2017; González-Múniz, Martín-Martínez, and Bonache 2016; Bautista-Expósito et al. 2018). Some studies reported proline, asparagine, glycine, and serine were the most common amino acids in ACE-inhibiting bioactive peptides of bean proteins (Yust et al. 2003; Valenzuela-García et al. 2017). Yust et al. (2003) also demonstrated all fractions with ACE I potency extracted from chick pea's protein were rich in hydrophobic amino acids and contained the amino acid methionine.

Typically, peptides with hydrophobic amino acid or hydrophobic isoleucine residue at the third position of C-terminal are the most favorite competitive inhibitors because of forming the hydrogen bonds between their C-terminal part and the ACE catalytic site (González-Múniz, Martín-

Martínez, and Bonache 2016; Nawaz et al. 2017). The presence of branched-chain amino acids in protein also show the ACE I activity and its effect is probably as same as hydrophobic sides (Aluko et al. 2015; Manzanares et al. 2019). Moreover, the interaction between the net hydrophilic of amino acids and zinc cation in the ACE active part could enhance ACE inhibition (Aluko et al. 2015). A recent study reported that the existence of charge amino acid e.g. lysin and argenin at C-terminus could enhance ACE I activity (Valenzuela-García et al. 2017). Bautista-Expósito et al. (2018) demonstrated that peptides with Phe, Ile, Arg, Lys or Leu in the C-terminal tripeptide had high ACE inhibitor activity (ACE%=96%).

Based on Manzanares et al. (2019) study, one important factor to determine the kind of amino acids to show ACE I potency is a length of peptides. For example, the greatest amino acid residues for the C-terminus of dipeptides are both chains sides and hydrophobic side chains and tripeptides are aromatic amino acids. The position of acid amine in other parts of peptides could be considered as another factor.

Although there are many studies about ACE I activity of food-derived bioactive peptides, the relationship between their structure and the ACE I activity has not yet been fully established.

## Germination

The sprouting or germination of seeds involves several metabolic activities within the seed caused to produce simpler compounds from storage proteins and other compounds (Saleh et al. 2018; Wu and Xu 2019). This process makes important changes in the biochemical, nutritional and sensory characteristics of legume seeds, mainly due to seed's enzymatic activity engaging in the hydrolysis of protein and starch. As a result, significant differences are made within legumes after and before germination (Gan et al. 2017; Mamilla and Mishra 2017; Khosravi, Razavi, and Fadda 2020). These changes depend on germination conditions such as temperature, soaking, time, humidity, light, and elicitor (Bubelov, Sumczynski, and Salek 2017; Yi-Shen, Shuai, and FitzGerald 2018). However, kind of seeds directly affect the seeds radicle and cotyledons developing toward germination time (Figure 2) (Paucar-Menacho, Berhow, and Mandarino 2010; Huang, Cai, and Xu 2014; De Souza Rocha et al. 2015)

### Bean germination

Germinated bean could break down some of seed storage proteins and release essential amino acids and bioactive peptides with ACE I, and DPP-IV I activity (De Souza Rocha et al. 2015; López-Barrios, Antunes-Ricardo, and Gutiérrez-Urbe 2016; Sritongtae et al. 2017). In vivo and in vitro studies also showed that bean peptides can inhibit some enzymes related to chronic diseases, hypertension and type-2 diabetes like dipeptidyl peptidase IV (DPP-IV),  $\alpha$ -amylase, ACE and  $\alpha$ -glucosidase (Kehinde and Sharma 2018; Los

et al. 2018). López et al. (2016) suggested the number of peptides increased after germination in the black bean (*Phaseolus vulgaris* L.). Chel-Guerrero et al. (2012) also reported that the germination process for 48 h significantly increased the protein content of the lima bean (*Phaseolus lunatus*) flour by 11.5%. These results were in agreement with Sritongtae et al. (2017) report that demonstrated free amino acids increased after rice bean (*Vigna umbellata*) germination. Moreover, some monitored anti-nutritional compounds decreased during germination (De Souza Rocha et al. 2015).

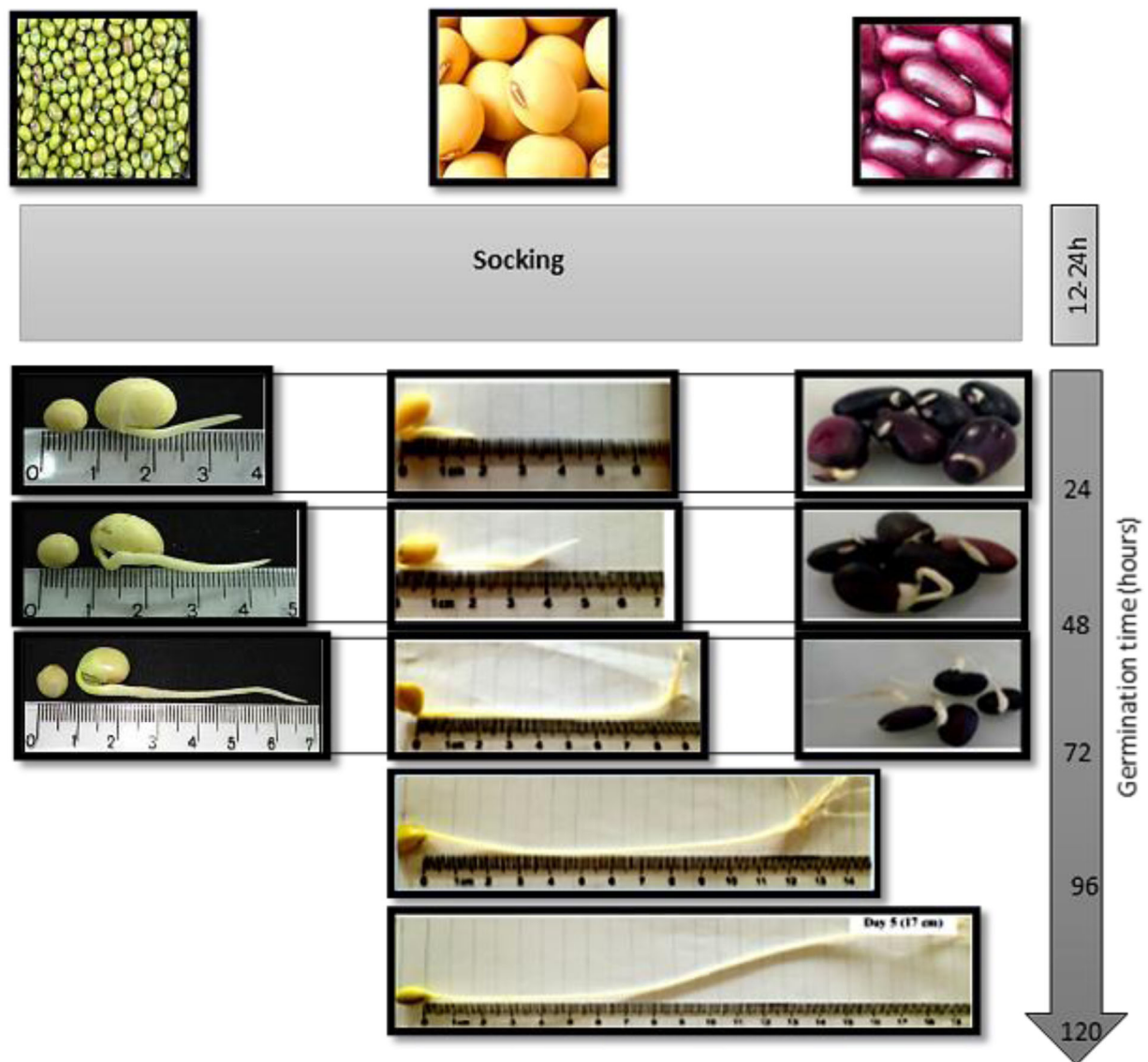
Effects of germination on bioactive peptides greatly vary according to the beans species, cultivars, germination conditions (temperature, light, moisture and germination time), and even separation methods for the analysis of the fractions (De Souza Rocha et al. 2015). For example, the use of HPLC fractionation for purifying the peptides could inhibit DPP-IV and may improve the IC<sub>50</sub> value (Harnedy, O'Keeffe, and FitzGerald 2015).

The germination time is one of the important factors to produce antihypertension peptides in the bean (Chel-Guerrero et al. 2012) and is between one to 5 days (Chel-Guerrero et al. 2012; De Souza Rocha et al. 2015; López et al. 2016). In most studies, protein content tends to increase by time (De Souza Rocha et al. 2015; López et al. 2016). López et al. (2016) reported that threonine, proline, and methionine contents were increased during 1–5 days of germination in black beans. Germination for 48 h increased protein content, too (Chel-Guerrero et al. 2012).

Although the presence of ACE I compounds after germination has been reported in some studies, the germination process may not always lead to the production of the ACE I activity peptides in bean according to Chel-Guerrero et al. (2012). They reported that the optimum ACE I activity in the un-germinated bean's treatments with IC<sub>50</sub> value between 0.56 and 2.11 mg/mL was more than germinated seeds, but the best ACE I activity gained by using sequential hydrolysis with pepsin-pancreatin for 1 h at a 1/10 E/S ratio (pepsin/pancreatin). De Souza Rocha et al. (2015) reported that simulated gastrointestinal digestion of the non-germinated and non-hydrolyzed sample (G0-0h) produced bioactive peptides by DPP-IV inhibitor potency (IC<sub>50</sub> 1.2mgSP/mL), in compared to the germinated common bean. According to these results, other processing such as alcalase hydrolysis could be applied toward bean germination to get the highest amount of bioactive peptides (Chel-Guerrero et al. 2012; De Souza Rocha et al. 2015).

### Lentil germination

Lentil germination significantly modifies the polyphenolics, produces smaller fragments via proteins and complex carbohydrates enzymatic breakdown, and enhances health content of nutritional value and ACE I bioactive peptides (Bamdad et al. 2009; Karakaya et al. 2016; Lopes, 201López et al. 62016; Jamdar, Rajalakshmi, and Marathe 2017). Ghumman et al. (2016) reported that lentil germination decreased high molecular weight (HMW) polypeptides of 80, 69, 60, 58, 55,



**Figure 2.** The effect of germination time on development of their radicle and cotyledons after 24 h, 48 h, 72 h, 96 and 120 h. 1. Mung bean, 2. Soybean, 3. Beans (Pauca-Menacho, Berhow, and Mandarino 2010) (Huang, Cai, and Xu 2014) (De Souza Rocha et al. 2015).

45, 37 and 33 kDa and increased low molecular weight (LMW) polypeptides of 19 and 14 kDa.

Most researchers have reported that the best temperature and time for Lentil germination is 30 °C (Karakaya et al. 2016) for 5 days or 20 °C (Bartolome, Estrella, and Hernandez 1997; Bamdad et al. 2009; Peñas et al. 2015) for 8 days. Bamdad et al. (2009) demonstrated that by increasing germination time, more peptides with a lower molecular weight and the ACE I properties isolated from lentil and the best result (ACE I%=70%) revealed after 5 days. Mamilla and Mishra (2017) demonstrated that red lentil germination at 40 °C could show higher ACE I activity (ACE I%=79.13%) rather than germination at 30 °C (ACE I% 48.80%).

The application of chemical elicitors during germination could also enhance the nutritional quality e.g. the phytochemical content, antioxidant, and potential antihypertensive activities in lentil sprouts (Peñas et al. 2015; Jamdar, Rajalakshmi, and Marathe 2017). Researches showed that elicitors such as glutamic acid, ascorbic acid, folic acid, glutamic acid with chitosan, ascorbic acid with chitosan and

folic acid with chitosan could increase the ACE inhibition of sprouts. However, some studies showed that using glutamic acid and ascorbic acid decreased the ACE inhibition of sprouts (Peñas et al. 2015; Liu et al. 2019). Peñas et al. (2015) used elicitors (500 μM ascorbic acid, 50 μM folic acid, 5 mM glutamic acid and 50 ppm chitosan in 5 mM glutamic acid) during lentil germination up to 8 days for enhancing germination rate, and the accumulation of GABA, phenolic compounds and ACE I activity. They reported that ACE I activity of lentil sprouts with ascorbic acid (IC<sub>50</sub> 9.5 μg peptides/mL) was as same as water (IC<sub>50</sub> 9.8 μg/mL), while higher GABA content was gained by chitosan/glutamic acid. Although some studies illustrate the effect of germination condition role to exhibit ACE I activity, more studies need for determining best condition.

### Pea germination

Germination also uses to improve the nutritional quality of pea by releasing high DPP-IV and ACE inhibition bioactive



**Table 3.** The effect of different legumes germination on ACEI potency.

		ACE I Activity (IC <sub>50</sub> ) mg/ml					
		DR	SK	G 1D	G 2D	G 3D	SKCK
Chickpea	Non-IVPD	ND	ND	ND	3.0	2.8	ND
	IVPD	0.7	0.6	0.6	0.6	0.6	0.6
Cowpea	Non-IVPD	ND	ND	ND	ND	ND	ND
	IVPD	0.8	0.7	0.7	0.7	0.6	0.6
Black pea	Non-IVPD	2.7	4.3	2.9	1.6	3.9	3.5
	IVPD	0.7	0.5	0.6	0.7	0.7	0.7
White pea	Non-IVPD	2.8	2.4	3.1	2.0	1.2	ND
	IVPD	0.3	0.2	0.2	0.2	0.3	0.2

ND: No inhibitory activity was detected (i.e., IC<sub>50</sub> > 5 mg/ml); IVPD: In vitro protein digestion; N-IVPD: Before in vitro protein digestion

DR: Dry, SK: Soaked, G1D: Germinated 1 day, G2D: Germinated 2 days, G3D: Germinated 3 days, SKCK: Soaking followed by cooking (Jamdar et al. 2017)

compounds (De Souza Rocha, Hernandez, and Chang 2014; Ma, Boye, and Hu 2018). Naturally, storage globulin protein breakdown by catalyzing proteolysis and releasing low molecular mass peptides during germination (De Souza Rocha, Hernandez, and Chang 2014; Jamdar, Rajalakshmi, and Marathe 2017).

The pea germination is usually carried out at 25–30 °C for 24–72 h (De Souza Rocha, Hernandez, and Chang 2014; Ma, Boye, and Hu 2018). Jamdar, Rajalakshmi, and Marathe (2017) evaluated the effect of germination (24, 48, and 72 h) and other processing conditions (soaking and cooking), separately or together, on ACE I activity of legumes seed (cowpea (CWP), black pea (BLKP), white pea (WHTP) and chickpea(CHKP)). Except for chickpea, the solubility of proteins increased by soaking and germination in all the legume seeds. The phenolic content decrease by soaking (20–60%) and cooking, but germination could slightly increase them. The highest ACE I potency showed in the white pea with the IC<sub>50</sub> value of 0.2–0.3 mg/ml. They did not report significant differences between ACEI activity at different times. Briefly, the rank of ACEI activity in different legumes were white pea > black pea > cowpea > chickpea (Table 3). As a conclusion, germination could enhance ACE I activity by increasing free phenolic (FP) and proteolysis of the protein in legumes.

Besides all these reports, Jamdar, Rajalakshmi, and Marathe (2017) demonstrated that although germination enhanced the solubility of proteins in all the legume seeds, but could not affect the ACE I potential of the seeds and dry legumes (control samples) had the highest antioxidant and ACE I activity.

## Fermentation

Fermentation is an old method for food preservation and also contributes to increase of the radical scavenging activity of both raw and processed legumes (Bartolome, Estrella, and Hernandez 1997; Bautista-Expósito et al. 2018; De Pasquale et al. 2019). Kind of microbial culture and environmental fermentation condition e.g. temperature, time, aw, and pH could affect the number of secreted-proteases to hydrolyze protein (Sanjukta and Rai 2016; Sanlier, Gökçen, and Sezgin 2017; Hajfathalian et al. 2017; Leblanc, Luerce, and Miyoshi 2018) and suitable microbial digestion and its enzyme

activity could happen in the best environmental conditions (Bautista-Expósito et al. 2017; Limón et al. 2015). Kind of inclusion microbe is also the most important factor to determine the best fermentation conditions. As a result, microbial culture, enzyme activity, and environment condition are three main factors in grain fermentation which are in correlation to each other to increase the free amino acids concentration and protein digestibility, the degradation of phytic acid, tannins and raffinose, and decrease the ACE and trypsin inhibitory activity and starch hydrolysis index (Duenas et al. 2005; Kapravelou et al. 2014; Bautista-Expósito et al. 2018; Gobetti et al. 2019; De Pasquale et al. 2019). The parameters including kind of inoculation starter, and fermentation environmental condition which affect the releasing of ACE I compounds during fermentation have been shown in Figure 3. Based on figure, the time of fermentation could change from 2 h to several weeks. Determining best temperature and pH of fermentation are related to inoculation starters growth and it change from 30 °C to 42 °C and 4–9, respectively.

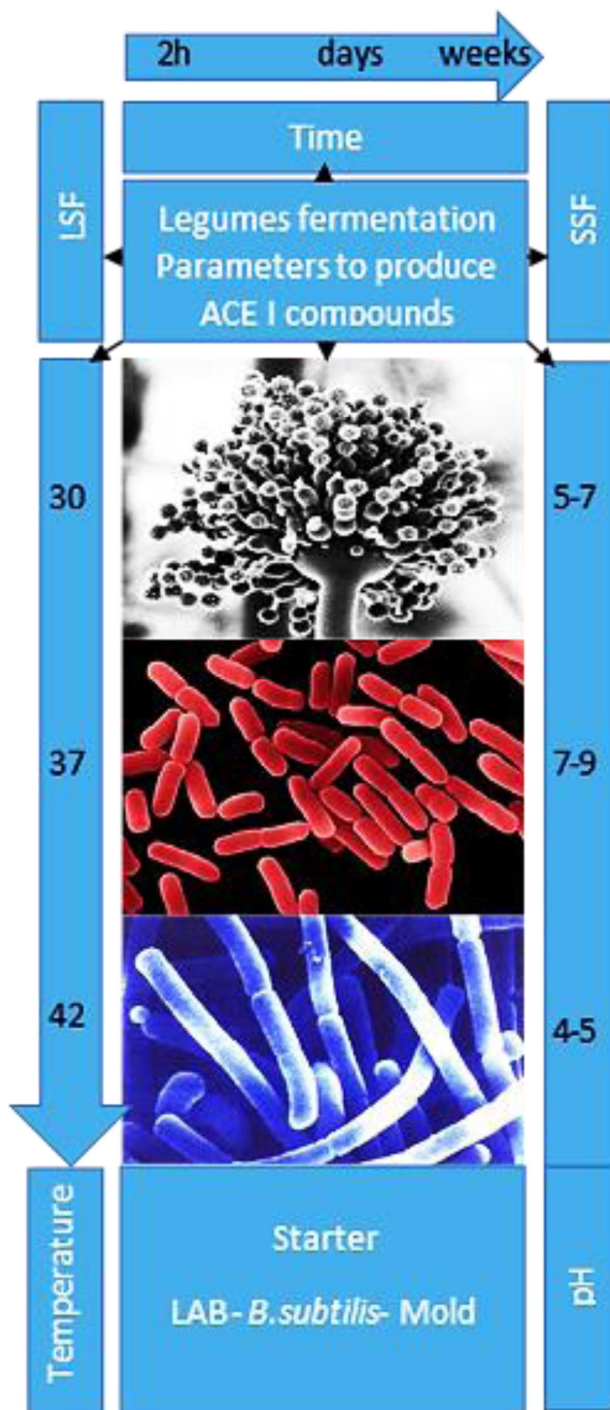
However, it should be considered that determining the best fermentation condition depends on the kind of peptides needing for inhibiting target enzyme activity. For example, the highest  $\alpha$ -amylase inhibitory activity fraction with a molecular mass of 3.5–7 kDa was obtained after fermentation at 22 °C for 3 h, however, the optimal fermentation conditions for releasing the highest lipase or ACE inhibitory peptide (IC<sub>50</sub> 1.19 and 0.28 mg mL<sup>-1</sup>, respectively) with a molecular mass of 3.5–7.0 kDa were 30 °C and 3 days (Jakubczyk et al. 2017).

According to Limón et al. (2015) the legume content, the fermentation conditions, different manner to the formation of ACE I compounds by the starter strains used during fermentation may be the reasons for the differences found between different studies.

## Effect of fermentation parameters on releasing ACE I compounds

### The effect of microbial culture

Kinds of natural and inoculation microbial culture such as lactic acid bacteria and *Bacillus* strains affect the enzyme activity, and as a result, the structure and amount of peptides with ACE I potency released by proteins degradation (Torino et al. 2013; Limón et al. 2015; Lee, Lai, and Wu 2015; Bautista-Expósito et al. 2018; Ma, Boye, and Hu 2018). So, the choice of starter cultures is one of the main steps for fermentation that has been widely studied (Suwanmanon and Hsieh 2014; Rui et al. 2015; Jakubczyk et al. 2017). According to studies, the proteolytic bacteria such as *Bacillus subtilis* spp. (*B.subtillus*), lactic acid bacteria (LAB) species e.g. *Lactococcus* (L.) *lactis*, *Lactobacillus* (Lb.) *helveticus*, and *Lb. delbrueckii* ssp. *Bulgaricus*, and molds can liberate bioactive peptides from legumes/pulses proteins (Teneva et al. 2018). Jakubczyk et al. (2017) reported the fermentation of bean proteins by inoculating *Lb. plantarum* 299v and in vitro digestion not only showed ACE I activity but also inhibit lipase and  $\alpha$ -amylase activity. Those results were in



**Figure 3.** The parameters which affect the releasing of ACE I compounds during fermentation includes: kind of inoculation starter and fermentation environmental condition: time and temperature change between 30 and 42°C and 18 h-several weeks, respectively. pH: the best pH for inoculation starters growth 1: Mold (*Aspergillus oryzae*), 2: *Bacillus subtilis*, 3: LAB.

agreement with Bautista-Expósito et al. (2018) studies about the fermentation of lentil by *Lb. plantarum*. De Pasquale et al. (2019) also reported fermentation with *Lb. plantarum* MRS1 and *Lb. brevis* MRS4 further enhanced the nutritional properties of processed legume flours. Torino et al. (2013) also reported that fermentation by *Lb. plantarum* was an adequate process for improving the concentration of phenolic compounds in fermented cowpea flour.

Besides the kind of fermentation inoculum microbe, the different species of the same LAB genus could also release different ACE I activity compounds according to Rui et al. (2015). They reported the fermented navy bean milk (NBM) extracts by *Lb. plantarum* B1-6 exerted the lowest IC<sub>50</sub> value (21 µg protein/ml) rather than other LAB containing including *Lb. bulgaricus*, *Lb. helveticus* MB2-1, and *Lb. plantarum* 70810. However, compared to the unfermented samples, all fermented NBM by *Lb. plantarum* 70810, *Lb. plantarum* B1-6 and *Lb. bulgaricus* showed higher ACE I activity with the IC<sub>50</sub> values of 109, 108, and 101 µg protein/ml, respectively.

LAB population is another important factor because the increment of proteolytic activity by the growth of the LAB population enhances the accumulating of ACE I peptides during fermentation (Limón et al. 2015).

Although LAB inoculation for legumes fermentation shows healthy effects, it seems there are some limitations for using them. First, the low proteolytic activity of the most LAB makes hard releasing sufficient bioactive peptides from legumes proteins. Secondly, pH reduction during the LAB fermentation may affect the solubility of legumes' proteins and phenolic, and reduce these bioactive compounds functional properties (Bautista-Expósito et al. 2017; Bautista-Expósito et al. 2018). So, using other microbial cultures and/or combinations of them together could enhance bioactive peptides with ACE I potency (Torino et al. 2013; Suwanmanon and Hsieh 2014). According to Torino et al. (2013), the natural microbial population exhibited higher proteolytic activity than *Lb. plantarum*. *B. subtilis* and could also significantly raise the total phenolic content (TPC) and slightly increased the free amino acids of lentils after 48 and 96 h solid state fermentation (SSF). Ma, Boye, and Hu (2018) indicated the combination of several LAB cultures e.g. *S. thermophiles*, *Lb. bulgaricus*, and *Lb. Acidophilus* to yellow field pea reduced anti-nutritional ingredients and produced bioactive peptides. Additionally, Suwanmanon and Hsieh (2014) evaluated the changes of arterial blood pressure in spontaneously hypertensive rats (SHR) by the short-term bean fermentation via inoculation *B. subtilis* B060 and demonstrated that fermented beans showed ACE I activity. This result was in agreement with the Lee, Lai, and Wu (2015) that reported both systolic blood pressure (21 mmHg) and diastolic blood pressure (30 mmHg) in SHR were improved by water extracts of pigeon pea fermented by *B. subtilis* 14715 which also showed the highest nattokinase (serine fibrinolytic enzyme) activity between different variety of *B. subtilis* named *B. subtilis* 14714, *B. subtilis* 14716, and *B. subtilis* 14718. In contrast to these reports, Torino et al. (2013) reported that *Lb. plantarum* could release higher bioactive compounds with ACE I (93% regardless of fermentation time) compared to *B. subtilis* (24% and 39% after 48 and 96 h, respectively). As a matter of fact, the difference between ACE I potency of peptides during legumes fermentation might be related to the different kinds of proteases released by native LAB, *Lb. plantarum* and *B. subtilis* (Torino et al. 2013; González-Múniz, Martín-Martínez, and Bonache 2016; Bautista-Expósito et al. 2017; Bautista-Expósito et al. 2018). Except for LAB and *B. subtilis*,

*Aspergillus niger* (*A. niger*) (KR535626) could also release peptide with ACE I potency according to Nawaz et al. (2017) demonstration.

Results showed that the combination of fermentation with other processing e.g. protein hydrolysis could improve the beneficial health effects of pulses (Bautista-Expósito et al. 2018).

### Effect of fermentation condition

**Effect of time and temperature.** Time which has been widely studied is an important parameter for legumes fermentation to determine the content of bioactive compounds such as ACE I and GABA (Torino et al. 2013; Rui et al. 2015; Limón et al. 2015; Bautista-Expósito et al. 2017). Torino et al. (2013) reported that the antihypertensive effect of natural lentil fermentation (NF) at 96 h was higher than NF at 48 h. This result was in agreement with Jakubczyk et al. (2017) and Rochín-Medina et al. (2015) that reported the best fermentation time for gaining the highest ACE I compounds was 72 and 100 h, respectively. In the contrast with these studies, Limón et al. (2015) demonstrated that ACE I activity increased during the 48 h of fermentation, whereas no further improvement occurred at 96 h of fermentation. Rui et al. (2015) also reported that the highest content of ACE I activity of peptides during fermentation by inoculation *Lb. plantarum* strains were obtained within 6-hour fermentation and the optimum fermentation periods for *Lb. plantarum* 70810, *Lb. plantarum* B1-6 and *L. bulgaricus* at 2 h, 3 h, and 5 h fermentation, respectively. There are also some other researches demonstrating that time had a negative effect on ACE I activity of fermented seeds whereas show although a positive effect on protein hydrolysis (Rui et al. 2015; Bautista-Expósito et al. 2017). Regardless to these few studies about short-term fermentation, much more reports demonstrated that increasing time during fermentation simultaneously enhances the ACE I compounds (Tabera et al. 1995; Torino et al. 2013; Rochín-Medina et al. 2015; Jakubczyk et al. 2017).

Another parameter to determine the best condition for releasing ACE I compounds is the temperature (Torino et al. 2013; Jakubczyk et al. 2017; Bautista-Expósito et al. 2018). Kind of inoculation starter determines the best fermentation temperature, however, according to studies, it generally varies between 28 to about 37 °C (Tabera et al. 1995; Torino et al. 2013; Jakubczyk et al. 2017; Bautista-Expósito et al. 2018). Rochín-Medina et al. (2015) reported that bean's solid-state bioconversion (SSB) by *Rhizopus oligopus* (*R. oligopus*) at 38 °C was the best temperature for obtaining the functional flour with ACE I properties. Observational studies indicate that the best temperature for *Lb. plantarum* and *B. subtilis* incubation in lentil is at 37 °C and 30 °C, respectively (Torino et al. 2013; Bautista-Expósito et al. 2018). However, Jakubczyk et al. (2017) reported the optimal fermentation temperature for bean seeds by *Lb. plantarum* 299v to release peptide fractions with the highest ACE I activity (IC<sub>50</sub> 0.28 mg/mL) was 30 °C. Additionally, Tabera et al. (1995) reported the minimum fermentation temperature (28 °C) used to achieve the maximum protein

content and the lowest tannin/catechin ratio. They naturally fermented lentil flour for 4 days at different temperatures (28 °C, 35 °C and 42 °C).

**The effect of pH and its controlling.** In general, the control of pH during fermentation leads to extensive proteolysis and protein degradation (Bautista-Expósito et al. 2017). The growth of lactic acid bacteria decreases pH during fermentation (Ma, Boye, and Hu 2018). This factor could negatively affect the ACE I peptides bind with the active site of ACE via decreasing the negative charge of hydrophilic peptides residue (Aluko et al. 2015). In addition, the acidic environment due to uncontrolled fermentation by LAB makes protein precipitation and enzyme inactivation (González-Múniz, Martín-Martínez, and Bonache 2016). Low pH of the medium may also decrease the growth rate of inoculation microbe, resulting in an extended length of the lag phase (Mousavi et al. 2013). This factor could also affect the solubility of phenolic compounds (Bautista-Expósito et al. 2017). This effect has been widely studied by Bautista-Expósito et al. (2017, 2018). They used *Lb. plantarum* with a commercial food-grade alkaline protease from *B. subtilis* (Savinase 16L, an alkaline protease derived) to control pH during lentil flour fermentation. Higher proteolytic efficiency and peptide content were determined at pH 8 and the increase of pH had a positive effect on peptide content. Additionally, they exhibited that combination of *Lb. plantarum* CECT 748 to Savinase-hydrolysis (LPHS) released higher peptides with ACE I potency (95.43%). However, this fact isn't general for releasing all bioactive compounds as Suwanmanon and Hsieh (2014) report. They showed acidic conditions for beans fermentation by *B. subtilis* could accumulate GABA. They demonstrated the decrease of activity of glutamate decarboxylase (optimal pH ≈ 7) and GABA transaminase (optimal pH = 7–10) of *B. subtilis* B060 in the acidic condition was main reason. GABA transaminase catalysis the transformation of GABA to succinic semialdehyde.

Briefly, the pH of the legumes' fermentation is one of the most dominant factors affecting the peptide content, and ACE inhibitor activity due to their effect on proteolytic efficiency of enzymes, and this is related to kind of inoculum starter, kind of legumes, and peptides inhibitors (Bautista-Expósito et al. 2017).

**The effect of fermentation method: SSF/LSF.** Two technologies used for fermentation are Solid State Fermentation (SSF) and Liquid State Fermentation (LSF) (Reyes-Bastidas et al. 2010; Rochín-Medina et al. 2015; Xiao et al. 2018). During SSF, many enzymes e.g. proteases, amylases, esterases, and cellulases are produced by microbes. These enzymes could hydrolyze protein, polysaccharide, lipid, and other macromolecules to produce new compounds and improve nutrition, flavor, and aroma by (Rochín-Medina et al. 2015; Nawaz et al. 2017; Xiao et al. 2018). In addition, higher contents of total and essential amino-acid might be produced due to the synthesis or transamination (Reyes-Bastidas et al. 2010). Considering to selection of suitable



strain and process parameters is crucial to the success of SSF processes (Maryam Hashemi et al. 2010). Xiao et al. (2018) found that the fermented red bean flour by SSF and LAB adversely to the non-fermented red bean showed ACE I activity with the  $IC_{50}$  value of 0.63 mg protein/ml. This result was in agreement with Rochín-Medina et al. (2015). They worked on black bean flour fermentation to enhance nutritional value, and antihypertensive potential by optimizing the SSB process inoculating *R. oligoporus*. They reported that the potential of ACE I activity significantly increased during this process with the range of the  $IC_{50}$  value of 95.57 to 0.0321 mg/ml. Additionally, the two ultra-filtered (UF) fractions (peptide fraction named F70, F71) collected from fermented pigeon pea by SSF showed ACE I potency (Nawaz et al. 2017). Reyes-Bastidas et al. (2010) suggested the unfolding proteins during SSF and facilitating the protease's access to protein structure could be the main reason for an increase in the fermented products' peptides with ACE I activity. Beside of SSF, a few studies indicated that ACE I compounds could be increased during LSF, too (Torino et al. 2013; Limón et al. 2015). The extracts of the lentil during LSF by *Lb. plantarum* (1–2% (v/v)) had higher ACE inhibition and free amino groups than SSF. Due to the high proteolytic activity of *B. subtilis* inoculated to SSF, this process exhibited higher proteolytic activity compared to LSF (Torino et al. 2013). Limón et al. (2015) also inoculated *Lb. plantarum* CECT 748 and *B. subtilis* CECT 39 into kidney beans using LSF or SSF, respectively. Kidney beans with LSF for 48 h showed the highest effects on ACE I. Two extracts of LSF phenolic compounds (NF48 and LPF48) exhibited quite similar  $IC_{50}$  values (41.63 and 39.17 lg protein/ml for NF48 and LPF48, respectively). They reported SSF kidney bean extracts could not show antihypertensive components.

Briefly, based on all studies, applied SSF for grains is more than LSF but more studies need to determined certainly (Reyes-Bastidas et al. 2010; Rochín-Medina et al. 2015; Nawaz et al. 2017; Xiao et al. 2018). Except for releasing ACE I activity compounds, use of low cost materials such as agricultural wastes as substrate and microorganisms growing on solid supports in the absence (or near absence) of free water to decrease the number of downstream steps are two main advantage of SSF process in comparison to LSF (Hashemi et al. 2011; Khosravi and Razavi 2020)

### Beans fermentation

Fermented bean and its flour may serve as a novel nutritional and anti-hypertension food because of phytochemicals or partial hydrolysis of proteins or/and other compounds and liberating ACE I components during fermentation due to the enzymatic activity of inoculation starters (Garcia-Mora et al. 2014; Rochín-Medina et al. 2015; Xiao et al. 2018). According to Durak et al. (2013) study, individual peptide fractions of bean's protein are a good source of bioactive compounds against antihypertension and prolamins which show the highest ACE I activity with  $IC_{50}$  of 0.17 mg/ml among all fractions. Additionally, fermentation

significantly affects the characteristics and amount of proteins in red beans. Cured protein content with fermentation was higher (25.81 g/100 g) than un-fermented seeds (23.61 g/100 g) (Xiao et al. 2018). According to Reyes-Bastidas et al. (2010) study, fermentation could eliminate the anti-nutritional factors of pulses and significantly increase common bean's in vitro protein digestibility (IVPD). Briefly, the bean seeds or bean flours should be processed due to eliminate the intrinsic anti-nutritional factors such as phytic acid, trypsin inhibitors, and others (Leblanc, Luerce, and Miyoshi 2018). Xiao et al. (2018) also demonstrated the amount of Hippuric acid (HA) liberated in the presence of fermented red bean (FRB) was significantly lower than the control treatments. The hippuryl-L-histidyl-L-leucine (HHL) is one of the ACE I measurement methods and the lower content of released HA in this method shows the stronger ACE I activity of the sample (Xiao et al. 2018). Besides bioactive peptides, Limón et al. (2015) suggested that catechins and flavonols showed the greatest influence on ACEI activity in the case of LSF and SSF, respectively.

Table 4 shows the effect of germination and fermentation on releasing ACE I compounds in beans.

### Lentil fermentation

Lentil fermentation is a method for increasing the bio-accessibility of complex polyphenols and proteins with antihypertensive and health promoting properties (Torino et al. 2013; Bautista-Expósito et al. 2018; Dhull et al. 2020). Dhull et al. 2020 also demonstrated that all minerals significantly increase in their concentrations upon red lentil fermentation except for K. Change of total protein content, in vitro protein digestibility and releasing of peptides may also increase during fermentation of lentils (Tabera et al. 1995). All these peptides are characterized by high bioavailability (Peñas et al. 2015). Derived peptides of the proteins such as legumin, vicilin, and convicilin may inhibit the ACE (Aslani et al. 2015; Bautista-Expósito et al. 2018; Barbana and Boye 2011). In addition, according to Jarpa-Parra (2017), some anti-nutrient compounds of lentil such as lectin can completely remove after the 72 h fermentation at 42°C. Table 5 shows the effect of germination and fermentation on releasing ACE I compounds in lentil.

### Peas fermentation

Processing through fermentation of pea provides an opportunity to increase protein digestibility, amino acid availability and nutritional value by releasing trypsin, chymotrypsin and ACE I activity compounds and reduced anti-nutritional factors (Lee, Lai, and Wu 2015; Awika and Duodu 2016; Ma, Boye, and Hu 2018; Kumitch et al. 2020). According to studies, the ACE I activity of cowpea (Dueñas et al. 2005; Awika and Duodu 2016), pigeon pea (Lee, Lai, and Wu 2015), and yellow pea (Ma, Boye, and Hu 2018) could increase via fermentation by *B. subtilis*, and LAB e.g. *Lb. plantarum* due throughout releasing the phenolic and peptides composition. Generally, enhances proteolytic activity and degree of soluble



**Table 4.** Effects of germination and fermentation on releasing bean's antihypertension compounds.

Compounds	Germination/Fermentation (conditions, inoculated microbe)	Effects	IC <sub>50</sub> or ACE% /Sequences peptides/ Molecular weight	Ref
NR*	Black beans germination	1- Increasing Peptides derived of cell wall proteins 2- increasing proline and methionine contents	NR*	López-Barrios et al. (2016)
NR*	Rice beans germination	Increasing amounts of free amino acids	NR*	Sritongtae et al. (2017)
NR*	Germination of green and white faba beans	increasing the free amino acid contents	NR*	Kapavelou et al. (2014)
Bioactive peptides	Germination and enzyme hydrolysis with Pepsin-pancreatin	1- increasing amount of available protein 2- significant increase of ACE I	IC <sub>50</sub> = 0.250 – 0.692 mg/mL	Chel-Guerrero et al. (2012)
Bioactive peptide	Germination and enzyme hydrolysis of common bean proteins with alcalase	1- no significant difference between germinated and the non-germinated samples in terms of $\alpha$ -amylase inhibitor 2- not seen improvement in the IC <sub>50</sub> by either germination or alcalase hydrolysis	RGPLVNPDPKPFL IC <sub>50</sub> =1.2mgSP/mL	De Souza Rocha et al. (2015)
Bioactive peptides	fermentation by <i>Lb. plantarum</i> 299v and in vitro digestion	1- releasing ACE I activity peptides 2- the highest lipase or/and ACE I activity reached at 30 °C and 3 days fermentation	INEGSLLLPH FVVAEQAGNEEGFE SGGGGGVAGAATASR GSGGGGGGGFGGPRR INEGSLLLPH GGYQGGGYGGNSGGGYGNRG GSGGGGGSSSGRRP GDTVTFEFDTLFSR Molecular weight= 3.5–7.0 Kd	Jakubczyk et al (2017)
$\gamma$ -aminobutyric acid (GABA) and natto kinase activity	Fermentation by <i>B.subtilis</i> B060	probably a successful strategy for producing a functional food with antihypertensive activity	NR*	Suwanmanon and Hsieh (2014)
Phenolic (NF48 and LPF48) and GABA	kidney beans fermentation by <i>Lb. plantarum</i> ATCC 14917 (SSF and LSF)	Obtaining ACE I activity compounds in water-soluble extracts via LSF	NR*	Limón et al. (2015)
Bioactive peptide	Fermentation of red bean flour by SSF and LAB	1-fermented red bean showed ACE I activity 2- the amount of proteins in red beans changed by fermentation 3- increasing amount of total amino acid and total essential amino acids	IC <sub>50</sub> = 0.63 mg protein/mL	Xiao et al. (2018)
Essential amino acids	SSF of common red beans by inoculation of <i>R. oligosporus</i> NRRL 2710	1- enhancing the Ile, Val, Thr, total aromatic (Phe - Tyr) and total sulfur (Met - Cys) amino acids 2- increasing common bean's In vitro protein digestibility	NR*	Reyes-Bastidas et al. (2010)
Bioactive peptide	fermentation black bean flour by solid-state bioconversion (SSB) process using <i>R.oligosporus</i>	1- improving antihypertensive potential 2- increasing the calculated protein efficiency ratio (from 1.59 to 2.40)	changing IC <sub>50</sub> value from 95.57 to 0.0321 mg/mL	Rochín-Medina et al. (2015)
Bioactive peptide	Fermentation bean by <i>Lb.bulgaricus</i> <i>Lb.helveticus</i> MB2-1 <i>Lb. plantarum</i> B1-6 <i>Lb. plantarum</i> 70810	1- higher ACE I activity in all fermented NBM compared to the unfermented ones 2- the lowest IC <sub>50</sub> in peptides gained by <i>Lb. plantarum</i> B1-6 inoculation	the lowest IC <sub>50</sub> value= 21 $\mu$ g protein/ml	Xin Rui et al. (2015)

NR: the abbreviation of Not Reported

protein hydrolysis (DH) upon peas e.g. chickpea fermentation is one of the main reason (Xing et al. 2020). Nawaz et al. (2017) reported that the F70 fractions of fermented pigeon pea which was made by SSF show high ACE I activity (85%) (IC<sub>50</sub> value: 9  $\mu$ g/ml). In addition, Ma, Boye, and Hu 2018 reported that fermentation improved the levels of essential amino acid including Val, Thr, Phe, Leu, Ile, and His in the pea. However, these changes are dependent to seeds

fermentation condition (Lee, Lai, and Wu 2015). Lee, Lai, and Wu (2015) examined the best time (8 h, 16 h, 24 h, 32 h, 40 h, and 48 h), temperature (30 °C, 35 °C, 37 °C, 40 °C, and 45 °C), and humidity (75%, 80%, 85%, 90%, and 95%) for inoculating *B. subtilis* in the pigeon pea. They observed that the optimal time, temperature, and humidity for releasing ACE I were 35 °C for 32 h at the relative humidity of 90%. Structural protein modifications via bacterial fermentation may also cause

**Table 5.** Effects of germination and fermentation on releasing lentil's antihypertension compounds.

Compound	Germination/Fermentation (conditions, inoculated microbe)	Effects	IC <sub>50</sub> or ACE% /Sequences peptides/ Molecular weight	Ref
Peptides	Comparison germination and digestion of lentil with whey protein	1- High ACE I activity in lentil after 5 days of germination 2- introducing lentil proteins as a good source of peptides with ACE I activity that can be released by germination or gastrointestinal digestion	ACE I% of 5-days germinated = 84.3% ACE I% of 5-day of germinated fractionation by RP-chromatography = 86.3%	Bamdad et al. (2009)
Peptides	effects of vegetable juice (VJ) and fermented vegetable juice (FVJ) fortified by germinated and sprout of lentil and cowpea	1- the ACE I effect of VJ was below 50%, and its IC <sub>50</sub> value could not be estimated 2- showing ACE I activity in FVJ 3- ACE I activity of FVJ were approximately 6.33 times higher than that of VJ	FVJ IC <sub>50</sub> value = 50 µg protein/ml ACE I% of FVJ= 80.2%	Simsek, et al. (2014)
Peptides	Evaluation of the effect of elicitation on the protein profile and ACE I activities of sprouted lentils	1- The application of elicitors did not negatively affect the germination of lentils 2- not significant changes in the protein pattern of germinated lentils 3- all elicited lentil sprouts inhibit the ACE activity	IC <sub>50</sub> = 9.5–11.9 µg peptides/ mL	Peñas et al. (2015)
Peptides	Germination of lentil at two different temperature (40 °C and 30 °C) and evaluating the effect of temperature on ACE I activity	higher ACE I activity in red lentil germination at 40 °C	ACE I% at 40 °C = 79.13% ACE I% at 30 °C = 48.80%	Mamilla and Mishra (2017)
Peptides	The effect of LSF and SSF of lentils for production of water-soluble fractions with antioxidant and antihypertensive properties LSF by natural LAB (NF) and <i>Lb. plantarum</i> (LP) SSF by <i>B. subtilis</i>	1 - exhibiting similar IC <sub>50</sub> values in NF and <i>Lb. plantarum</i> (LP) water-soluble extracts 2- more potency of ACE I activity in LSF of lentil extracts than lentil hydrolysate-protein 3- higher health-promoting potential against hypertension in LSF than SSF 4- improving ACE I activity of lentil extracts by NF 5- <i>LP</i> showed higher ACE inhibition than <i>B. subtilis</i>	IC <sub>50</sub> value of NF = 0.18 mg protein/ml IC <sub>50</sub> value of LP = 0.20 mg protein/ml IC <sub>50</sub> value of LSF= 0.44 mg protein/ml ACEI% of <i>L. plantarum</i> = 93% ACEI% after 96 h = 67.5% –92% ACEI% of <i>B. subtilis</i> after 48 h = 24% ACEI% of <i>B. subtilis</i> after 96 h = 39%	Garcia-Mora et al. (2014)
Peptides	pH-controlled of fermentation by <i>Lb. plantarum</i> CECT 748 and Savinase-hydrolysis together (LPHS) and separately for producing multifunctional lentil compounds	1- No significant differences in ACE I percentages between HS (enzymatic hydrolysis with Savinase) LP (fermentation with <i>Lb. plantarum</i> ) and LPHS (enzymatic hydrolysis + fermentation) 2- Most abundant peptides identified in fraction F1 collected from LPHS by size exclusion chromatography	ACE% of LP= 94.06% ACE% of HS= 93.05% ACE% of LPHS= 95.43% IC <sub>50</sub> of LP =0.38 mg/ml IC <sub>50</sub> of HS= 0.47 mg/ml IC <sub>50</sub> of LPHS= 0.39 mg/ml peptides identified in fraction F1 (ACE% of F1 = 96.00): SDQENPFIFK HGDPEER ATAFGLMK	Bautista-Expósito et al. (2018)
Peptides	identify peptides with ACE I activities from lentil proteins by Savinase	1- clarifying the relationship between structure and dual 2- antioxidant/ antihypertensive activity of lentil peptides	IC <sub>50</sub> of NSLTLPILRYL= 77 µM IC <sub>50</sub> of LLSGTQNQPSFLSGF = 118 µM IC <sub>50</sub> of TLEPNSVFLPVLLH: 118 µM	González-Múniz et al. 2016
Peptides	Fermentation using <i>Lb. plantarum</i> and Savinase 16 L at different pH (6.5–8.5) and times (5.5–30 h)	1- pH positively affected peptides, soluble phenolic compounds, and antioxidant activity 2- Time showed a positive effect on proteolysis and negatively affected ACE I activity of fermented lentil 3- Multivariate optimization led to high levels of peptides, soluble phenolics and bioactivity of fermented lentil at pH 8.5 and 11.6 h	ACE%= 46.6–95.2%	Bautista-Expósito et al. (2017)

LSF: Liquid State Fermentation

SSF: Solid State Fermentation

better accessibility of digestive enzymes to the substrate. Moreover, breaking down intact proteins by bacteria can increase the concentration of free amino groups (Xing et al. 2020). Table 6 shows the effect of germination and fermentation on releasing ACE I compounds in pea, chickpea, and cowpea.

### Germination and fermentation

According to studies, combination of germination and fermentation are cost-effective processes to increase bioactive

compounds and could serve as one strategy to nutraceutical enhancement of pulses (Bartolome, Estrella, and Hernandez 1997; Karakaya et al. 2016; Hiran, Kerdchoechuen, and Laohakunjit 2016). Ma, Boye, and Hu (2018) demonstrated that the fermentation of germinated peas improved nutritional properties and reduced anti nutrition ingredients such as tannin. Lee et al. (2018) also reported that compounds produced by fermentation of germinated black bean (GRB) with LAB can be solubilized in water and have high immunostimulatory activity. Simsek et al. (2014) also investigated the effect of both germination and fermentation to improve

**Table 6.** Effects of germination and fermentation on releasing pea's antihypertension compounds.

Compounds	Germination/ Fermentation (conditions, inoculated microbe/)	Effects	IC <sub>50</sub> or ACE% /Sequences peptides/ Molecular weight	Ref
Peptides	germination of cowpea, combined with enzymatic hydrolysis to the generation bioactive peptides with dipeptidyl peptidase IV (DPP-IV) inhibition activity	1- The non-germinated and 1 h alcalase hydrolysates showed the highest DPP-IV inhibition 2- Cowpea short time germination (24 h) and alcalase protein hydrolysis (1 h) can be produced peptides with high DPP-IV inhibition	IC <sub>50</sub> = 0.58 mg SP/mL	De Souza Rocha et al. (2014)
Peptides	Effect of processing conditions and in vitro protein digestion on bioactive potentials of legumes - soaking, germination at 24, 48, and 72 h) - soaking and cooking - in vitro protein digestion (IVPD)	1- the highest ACE I activity in white pea 2- germination slightly increased phenolic compounds 3- different time germination did not have an effect on ACE I activity	IC <sub>50</sub> values in the range of 1–5 mg/ml	Jamdar et al. (2017)
Peptides	Fermentation of pigeon pea with <i>A. niger</i>	1- extraction the novel ACE I octapeptide sequences (Val-Val-Ser-Leu-Ser-Ile-Pro-Arg) 2- strong and stable interaction with ACE and ACEI activity	IC <sub>50</sub> value of F70 (fraction 70) = 9 µg/ml and 85% of ACEI% Val-Val-Ser-Leu-Ser-Ile-Pro- Arg molecular mass= 869.53 Da	Nawaz et al. (2017)
Peptides	pea protein hydrolysis and in vivo test of effectiveness of antihypertensive peptides	ACE I properties	IFENLQN FEGTVFENG LTFPG IIPLEN LSSGDVVF  ACE I%=87.54% molecular mass= 877 Da ACEI%= 76.77% molecular mass= 999 Da ACEI%= 20.20% molecular mass= 534 Da ACEI%= 5.7% molecular mass= 698 Da ACEI%= 6.6% molecular mass= 724 Da	Aluko et al. (2015)

NR

\*: Not Reported.

the nutrient and ACE I activity of lentil preparing by the fermentation vegetable juice (FVJ) via *Lb. plantarum* containing lentils and cowpeas sprouts. They reported that ACE I activity and IC<sub>50</sub> values of FVJ were 80.2% and 50 µg protein/ml, respectively while ACE I effect of vegetable juice (VJ) was below 50% and approximately 6.33 times lower than FVJ (IC<sub>50</sub> value of VJ could not be estimated). Both germination and fermentation lead to significant changes in the phenolic compounds by improving bioactive compounds e.g. procyanidin-type compounds and phenolic compounds (Bartolome, Estrella, and Hernandez 1997)

Beside of all reports, further studies need to determine and identify the effect of combination fermentation and germination to release ACE I compounds in pulses.

## Conclusion

As described in this review, legumes' fermentation and germination are two good technologies to produce valuable and

nutritional compounds. These processes change the peptide profiles and increase the content of the low-molecular-weight peptides and polyphenol compounds. They also enhance the accessibility and bioavailability of compounds by digestive and hydrolysis them via different enzymes. Optimizing these processes is a fundamental factor to gain a high amount of ACE I activity or other bioactive compounds. Kind of starters, time, temperature, pH and aw are important factors for fermentation. For legumes' fermentation process, the temperature and humidity are often controlled between 28–37 °C and 90–95% in the neutral pH, respectively. While the duration of time is usually related to either kind of microbes and legumes. Time and temperature of germination are also two important factors to produce antihypertension peptides in pulses. In most studies, the protein content tends to increase by time and is usually carried out for 24–96 h and 25–30 °C. The application of chemical elicitors during germination could also enhance nutritional quality. However, more studies need to

determine the best germination condition. As a conclusion, fermentation is a common and inexpensive method to enhance bioactive compounds with ACE I activity and applying germination before it, could enhance these compounds.

## Acknowledgments

We would like to acknowledgment the university of Tehran.

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