RENIN-INHIBITORY BIOACTIVE PEPTIDES WITH ANTIHYPERTENSIVE PROPERTY: A REVIEW

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ABSTRACT

Blood pressure is regulated by the renin angiotensin aldosterone system (RAAS). Renin-catalyzes the conversion of angiotensinogen to angiotensin I and is the rate-limiting step of the RAAS pathway, which arguably makes renin inhibitors more better target for prevention, treatment and management of hypertension than angiotensin-converting-enzyme (ACE) inhibitors. Enzymatic hydrolysis of food proteins releases bioactive peptides that can interact with receptors, enzymes and molecules in the organism to promote health. Several studies have shown that these bioactive peptides could be exploited for management of hypertension which is a major risk factor for cardiovascular diseases (CVDs). Antihypertensive peptides are bioactive peptides derived from plant and animal sources with inherent potential to ameliorate hypertension by different mechanisms including scavenging of free radicals, reduction of cholesterol level, inhibition of angiotensin-converting enzyme (ACE) and renin enzyme activities. Although there is a lot of sufficient information on ACE-inhibitory and antioxidative peptides while literature on the potential role of renin-inhibitory peptides in the treatment of hypertension is limited. Thus, herein the present review primarily used ISI, SCOPUS and PubMed indexed journals containing experimental reports to elucidate the potential role of bioactive peptides in the management of hypertension through inhibition of rennin activity.

Keywords: Hypertension; Bioactive peptides; Renin inhibition; Mechanism of action.

INTRODUCTION

Blood pressure is simply defined as quantitative expression of the pressure in large arteries of the systemic circulation. The normal blood pressure for an individual is about 120/80 mm Hg while blood pressure which persistently exceeds 140/90 mm Hg is considered hypertensive. Hypertension is a risk factor for cardiovascular disease and stroke which in turn is one of the leading causes of death across the world (Nawaz *et al.,* 2017). Due to its asymptomatic nature coupled with lackadaisical attitude of some patients towards health and well-being, many hypertensive patients are not aware of it (Vincent-Onabajo *et al.,* 2017). Blood pressure is mainly controlled by renin angiotensin aldosterone system (RAAS). The RAAS pathway involves renin-catalyzed convertion of angiotensinogen to angiotensin I. Angiotensin I is then converted to angiotensin II via the action of angiotensin-converting enzyme (ACE). Angiotensin II mediates vasoconstriction and activates aldosterone release from adrenal gland (Nawaz *et al.,* 2017). Aldosterone promotes the expression of epithelial sodium channels which leads to sodium and water reabsorption resulting in the increased blood pressure (Nawaz *et al.,* 2017). In addition, oxidative stress was linked to hypertension particularly when the level of reactive oxygen species (ROS) exists in excess of antioxidant defense capacity of cells. In a physiological system, the imbalance between antioxidant defense mechanism and ROS production leads to oxidative stress and subsequent pathological conditions due to cellular injury [Heitzer *et al.,* 2001). ROS formation is associated with endothelial dysfunction, which is a key feature of cardiovascular diseases, including hypertension, atherosclerosis, and diabetes mellitus (Bedard et al., 2007). A previous study reported that ROS can oxidize low density lipoproteins leading to endothelial dysfunction which contributes to the formation of atherosclerotic plaque thereby increasing the likelihood of hypertension (Paudel *et al.,* 2016). There are plethoras of evidences linking the prevalence of hypertension to lifestyle and dietary factors (Daliri *et al.,* 2017; Gul *et al.,* 2015; Hernández-Ledesma *et al.,* 2011). Consequently, functional foods are emerging in response to the increased perception among consumers about the relationship between food and health benefits. In the past three decades, researchers have spent time and resources on the search for antihypertensive agents from potential natural antihypertensive agents in order to reduce the dependency on commercially available synthetic antihypertensive drugs often associated with negative side effects (Lin *et al.,* 2018). Food proteins can be enzymatically hydrolysed to produce bioactive peptides with antihypertensive potential (Ugwu *et al.,* 2019; Mada *et al.,* 2019). Bioactive peptides are active fragments contained in parent protein (Reddi *et al.,* 2016), but remain inactive until the parent protein is hydrolysed by cellular proteases (Hernández-Ledesma *et al.,* 2014; Mada *et al.,* 2017a), individually or combined (Mohanty

et al. 2016; Kumar *et al.,* 2016; Bamdad *et al.,* 2017; Chaudhari *et al.,* 2017) and also by microbial fermentation (Palaniswamy *et al.,* 2012; Koyama *et al.,* 2014; García-Tejedor *et al.,* 2015; Aguilar-Toalá *et al.,* 2017; Yahya *et al.,* 2017) or gastrointestinal digestion (Hernandez-Ledesma *et al.,* 2011; Alvarado *et al.,* 2019). Antihypertensive peptides are bioactive peptides derived from plant and animal sources with inherent potential to ameliorate hypertension through antioxidative effect and scavenging of free radicals (Mada *et al.,* 2017b; Lassoued *et al.,* 2015., Panth *et al.,* 2016; Wang *et al.,* 2017; Basilicata *et al.,* 2018; Pachaiappan *et al.,* 2018; Ugwu *et al.,* 2019), lowering of blood cholesterol level (Lammi *et al.,* 2016; Hernandez and de-Mejia, 2017), inhibition of ACE activity (Hernandez-Ledesma *et al.,* 2014; Capriotti *et al.,* 2015; Korczek *et al.,* 2018; Mirzaei *et al.,* 2018; Ugwu *et al.,* 2019) or inhibition of renin enzyme activity (Aluko, 2019; Lin *et al.,* 2017). Many research findings have continuously confirmed the antihypertensive effect of bioactive peptides and there is a lot of sufficient information on ACE-inhibitory and antioxidative peptides while literature on the potential role of renin-inhibitory peptides in the treatment of hypertension is limited. Renin-catalyzed conversion of angiotensinogen to angiotensin I and is the rate-limiting step of the RAAS pathway which makes renin inhibitors more better target for treatment and management of hypertension than ACE. Moreover, excessive plasma level of angiotensin I is a causative factor for hypertension because angiotensin I is the substrate used by ACE to produce angiotensin II, a vasoconstrictor (Fyhrquist & Saijonmaa, 2008). Therefore, bioactive peptides with renin-inhibitory effect can potentially lower blood pressure and provide relief from negative side effects associated with synthetic drugs. Consequently, the present review employed ISI, SCOPUS and PubMed indexed journals containing experimental reports to elucidate the potential role of bioactive peptides in the treatment of hypertension via inhibition of renin enzyme activity.

DISCUSSION
Renin Angiotensin Aldosterone System
The renin angiotensin aldosterone system (RAAS) plays a crucial role in the regulation of renal, cardiac and vascular physiology as well as the activation of hypertension (Ghazi and Drawz, 2017). Among the physiological mechanisms of hypertension, RAAS has attracted much scientific attention (Fig. 1). However, renin and ACE are the main enzymes involved in RAAS pathway (Guang *et al.,* 2012). For example once the kidney detects a drop in blood pressure, it secrets renin which in turn catalyses the conversion of angiotensinogen to angiotensin I, one of the substrates for ACE. Then ACE catalyses the conversion of angiotensin I to angiotensin II, a vasoconstrictor (Nawaz *et al.,* 2017). Angiotensin II promotes hypertension by increasing systemic vascular resistance and stimulating aldosterone release from the adrenal gland (Nawaz *et al.,* 2017). Renin is first synthesized as preprorenin in the juxtaglomerular epithelioid cells, then signal peptide is removed

by peptidase and preprorenin is converted to prorenin, an inactive form (Fig. 1). Like pepsinogen prorenin is activated by low pH and inactivated at neutral pH. Prorenin is then proteolytically converted into active renin by plasma kallikrein in a process known as proteolytic activation (Fig. 1), and then is stored in granules (Derkx *et al.,* 1987; Ames *et al.,* 2019). The release of renin granules is strictly regulated, making renin the rate-limiting step of the RAAS pathway in most species (Ames *et al.,* 2019). The ACE released from endothelial cells, converts angiotensin I to angiotensin II, then Angiotensin II acts at 2 different receptors; the angiotensin type-1 and type-2 receptors (AT-1R and AT-2R).Thus, the action of angiotensin II at the AT-1 receptor is responsible for increased sodium retention, vasoconstriction, increased salt consumption and aldosterone release from the adrenal gland of zona glomerulosa (Ames *et al.,* 2019). The interaction of angiotensin II at this receptor causes some of the diseases associated with chronic RAAS activation. Additionally, while AT-2 receptor is beneficial in the development of fetus, it is less relevant in healthy adults. Its stimulation leads to anti-inflammatory, anti-fibrotic, and vasodilatory effects and it might be upregulated in certain disease conditions (De-Mello, 2015; De-Mello and Frohlich, 2014; Bader, 2013). Aldosterone is an adrenal steroid hormone that binds to the mineralocorticoid receptors of the distal convoluted tubule. It increases the expression of epithelial sodium channels resulting in sodium and water reabsorption and possible hypertension (Briet and Schiffrin, 2010). Also, aldosterone mediates most of the mineralocorticoid activity of adrenal secretions, and regulates sodium, potassium, and body fluid balance (Hall and Guyton, 2010; Seelinger *et al.,* 2005). In addition, angiotensin II and increased extracellular K^+ concentration, amplify expression of the *CYP11B2* gene which encodes aldosterone synthase (Beuschlein, 2013). Aldosterone in turn acts via the mineralocorticoid receptor thereby modulating the expression of ion channels, pumps, and exchangers in epithelial tissues (Ames *et al.,* 2019). This leads to increased transepithelial Na^+ and water reabsorption as well as K^+ excretion. Interestingly, mineralocorticoid receptors are present in non-epithelial tissues such as the retina, vascular smooth muscle cells, macrophages, brain, myocardium, adipocytes and fibroblasts (Jaisser *et al.,* 2015; Marzolla *et al.,* 2014; Marzolla *et al.,* 2012; Funder *et al.,* 1989; Funder *et al.,* 1988). Aldosterone specifically mediates inflammation and affects energy metabolism in non-epithelial tissues (Marzolla *et al.,* 2014). Angiotensin peptides and aldosterone are equally synthesized in brain, blood vessels, kidneys, and the heart (De-Mello and Frohlich, 2014; Bader, 2010; Bader and Ganten, 2008; Dzau *et al.,* 2001). They play important roles in normal cardiovascular function and electrolyte-fluid homeostasis. However, they equally mediate abnormal remodeling in the tissues (Ames *et al.,* 2019). *In-vitro* experiment on cultured vascular smooth muscle cells and cardiomyocytes indicates that aldosterone upregulates ACE activity and angiotensin II-stimulated signal transduction, leading to increased tissue

activity of the RAAS (Harada *et al.,* 2001; Ullian *et al.,* 1994; Ullian *et al.,* 1993; Ullian *et al.,* 1992). Gradual and continuous activation of RAAS promotes and perpetuates heart failure, systemic hypertension, and chronic kidney disease (Ames *et al.,* 2019). Understanding the role of the RAAS in hypertension has grown over the past few decades and numerous therapeutic strategies aimed at blocking key components of the RAAS

pathway have been developed. Many synthetic antihypertensive drugs have been reported to cause adverse effects such as dizziness, dysgeusia, headache, angioedema, and cough (Daliri *et al.,* 2016), which has prompted the growing demand for antihypertensive peptides from food sources particularly due to their health-promoting effect and safety (Daliri *et al.,* 2017).
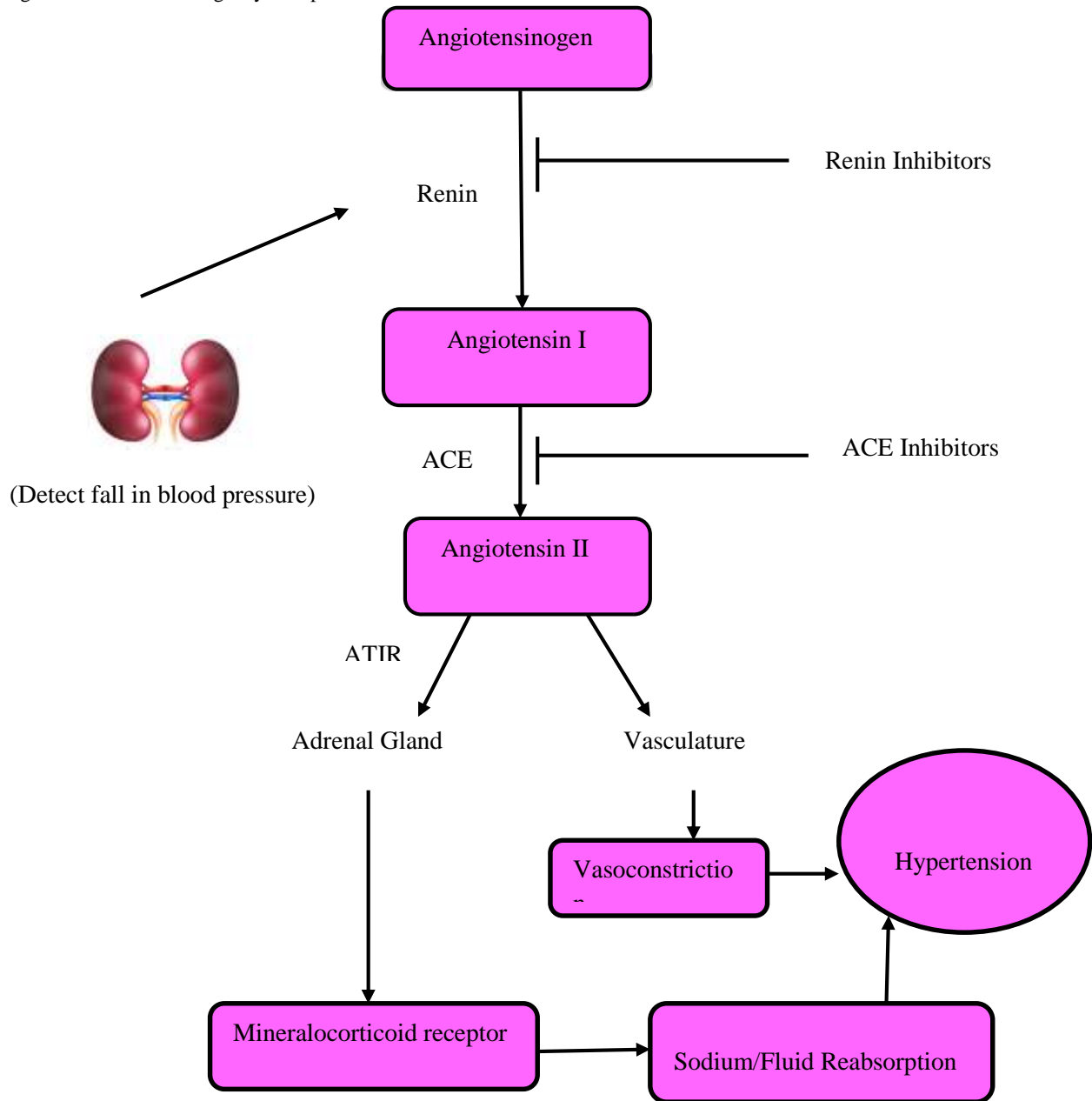
Figure 1: Renin angiotensin aldosterone system (RAAS) and its role in the regulation of blood pressure and hypertension. ATIR = Angiotensin type -1 receptor; ACE = Angiotensin Converting Enzyme.

Antihypertensive Peptides

Enzymatic hydrolysis or microbial fermentation of protein releases a large variety of bioactive peptides which can mimic peptide sequences acting in the organism as endogenous signals, or hormones (Hernández-Ledesma *et al.,* 2014). Generally, these bioactive peptides have high tissue affinity, specificity and efficiency, they can interact with enzymes and certain molecules in the organism to exhibits their primary function (Reddi, *et al.,*

2019; Mada *et al.,* 2019). The inherent physico-chemical characteristics of amino acid residues in the peptide sequences are responsible for their antihypertensive properties (Ugwu *et al.,* 2019). Antihypertensive peptides (Fig. 2) can act through inhibition of ACE and renin activity (Bleakley *et al.,* 2017; Zou *et al.,* 2016; Daliri *et al.,* 2017; Ugwu *et al.,* 2019), lowering of cholesterol level in the blood, prevention of oxidative damage and atherosclerosis thereby lowering blood pressure (Mada *et al.,* 2019) as outlined in (Fig. 2). Therefore, bioactive peptides with potential antihypertensive effect are gaining interest mainly due to lack of obvious adverse effects compared to orthodox antihypertensive drugs. Although, a previous study has shown that some bioactive peptides released by enzymatic hydrolysis or microbial fermentation can be potentially toxic or allergic (Liu *et al.,* 2020). Notwithstanding, bioactive peptides has been regarded as safe could be potentially employed for treatment and management of hypertension. Based on available literature a lot of studies on antihypertensive peptides focused on ACE inhibition while bioactive peptides with renin inhibition potential has been neglected despite the fact that it catalyzes the rate-limiting step of RAAS.
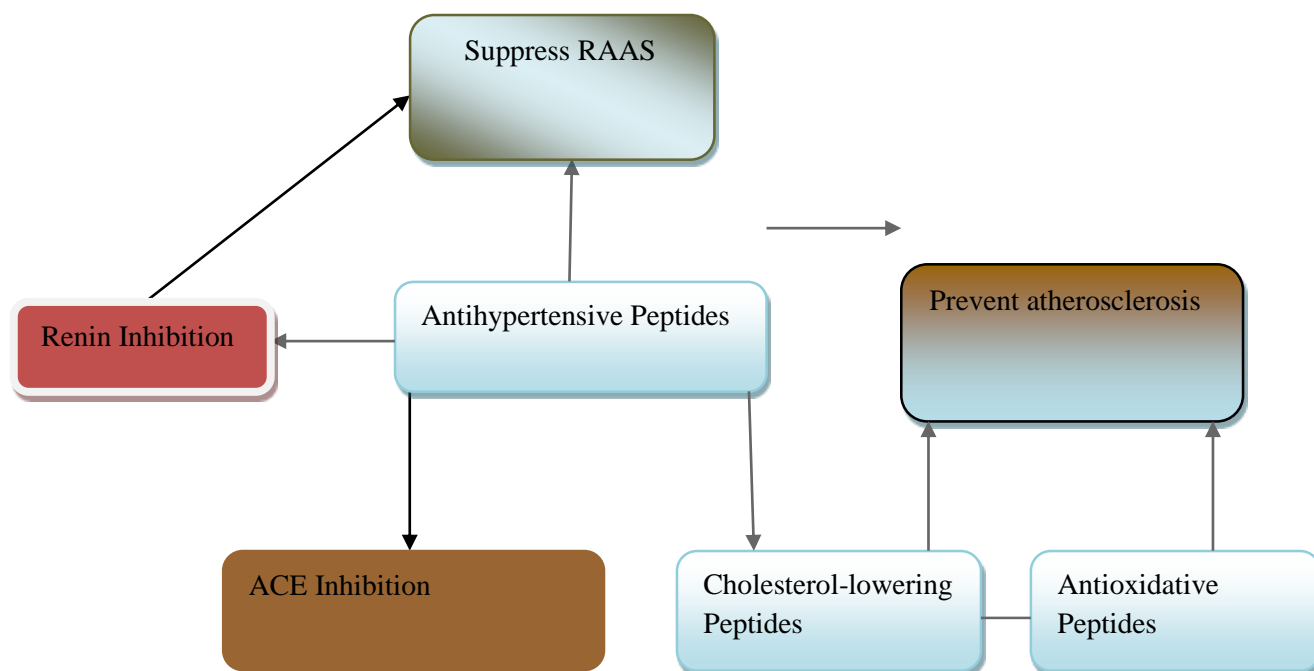

Figure 2: Different mechanisms through which bioactive peptides achieved antihypertensive effect. RAAS= Renin angiotensin aldosterone system, ACE = Angiotensin Converting Enzyme.

Renin Inhibitory Peptides

The primary function of renin is therefore to cause an increase in blood pressure, leading to restoration of perfusion pressure in the kidneys when volume of blood or sodium levels in the body are low or blood potassium level is high, then cells in the kidney release the enzyme renin (Ames *et al.,* 2019). The use of ACE inhibitor or in combination with other antihypertensive agents such as renin has always been considered the most effective blood pressure control measure. However, renin inhibition is potentially a better alternative for blood pressure regulation than ACE inhibition because unlike ACE, renin catalyzes the rate-determining step in the RAAS pathway (Duprez, 2006), by conversion of angiotensinogen which is present in the liver to angiotensin I. Then ACE found in the lungs metabolizes angiotensin I into angiotensin II. Subsequently angiotensin II causes blood vessels to constrict and thus leading to an increase in blood pressure (Ames *et al.,* 2019; Duprez, 2006). Moreover, ACE inhibitors and receptor blockers suppress the physiological negative feedback effect of angiotensin II on renin activity (Aluko *et al.,* 2019). Therefore, suppression of angiotensin II by ACE inhibitors may result in the increased level of renin in blood thereby activating the RAAS pathway to produce more angiotensin II and consequently reduce the activity of ACE inhibitors (Chen *et al.,* 2013). A Previous study has shown that oral administration of lactoferrin hydrolysate to spontaneously-induced hypertensive rats led to a reduction in plasma ACE activity but increased renin activity (Fernandez-Musoles *et al.,* 2013). Also, an ACE-inhibitory peptide (IW) and captopril caused increased expression of renin mRNA but lowered ACE activity in spontaneously-induced hypertensive rats (Martin *et*

al., 2015). This inverse relationship between ACE and renin activities could threaten the long-term health benefits of ACE inhibitors; hence co-administration of renin inhibitors may improve management of hypertension (Aluko *et al.,* 2019). Therefore, this also suggests administration of renin inhibitor as a single pill might not produce better antihypertensive effects.

Purification of crude peptides and its effect on renin activity
Crude peptides may show renin-inhibitory effect but the inhibitory activity increases with increase in purity of the crude peptides (Addar *et al.,* 2019). Upon enzymatic hydrolysis of protein with suitable proteases, followed by inactivation of the proteolytic enzymes and subsequent centrifugation produces crude peptides or peptide hydrolysates (Kumar *et al.,* 2016; Ugwu *et al.,* 2019), which can exhibit greater inhibitory effect than the unhydrolyzed proteins. However, further purification of crude peptides or peptide hydrolysates via s reversed phase-HPLC and ultrafiltration with membrane filters (<1 to 3KDa) techniques can generate fragments of bioactive peptides with greater inhibitory activity than crude peptides. Previous study by Ciau-Solis and coworkers enzymatically hydrolyzed Lima bean (*Phaseolus lunatus*) protein with one of two sequential enzymatic systems (pepsin-pancreatin or Alcalase®-Flavourzyme®), their findings revealed that membrane ultrafiltration of the hydrolysates produced fractions of different molecular weights and >3 kDa fraction of the pepsin-pancreatin hydrolysate had the highest ACE-inhibitory activity while the >3 KDa fraction of the Alcalase®-Flavourzyme® hydrolysate had the highest renin-inhibitory activity *in vitro* (Ciau-Solis *et al.,* 2018). Interestingly, they demonstrated that fractionation of hydrolysate using membrane filter of 3kDa enhanced renin inhibition when compared to the crude hydrolysates. For instance, alcalase-flavourzyme and pepsin-pancreatin hydrolysates showed 15.5% and 5.5% renin inhibitions respectively (Table 1), while further ultrafiltration with < 3kDa membrane filter the fractions obtained exhibited increased in renin-inhibitory effects from 13.7% to 31.7% (Ciau-Solis *et al.,* 2018). This is suggestive of a weak synergistic action among peptides in the crude peptide hydrolysate, hence more purification via ultrafiltration led to enhanced activity (Ciau-Solis *et al.,* 2018). The probable explanation to this observed effect could be due to lack of strong synergistic effects in the crude hydrolysate; hence membrane fractionation led to

isolation of low molecular weight bioactive peptides with higher renin inhibitory activity than the hydrolysate or high molecular weight (Aluko *et al.,* 2019).

Moreover, this data imply a single or individual pure peptide may exhibit better renin inhibitory activity than many peptides working together in a particular fraction due to antagonistic effect, which were ameliorated after ultrafiltration of the hydrolysate fraction into low molecular weight bioactive peptides. Though, in contrast to the above findings, Girgih and colleagues also investigated the antihypertensive effects of enzymatic hemp seed protein hydrolysate (HPH) and its peptide fractions. They digested hemp seed protein using sequential action of pepsin and pancreatic enzymes to mimic gastrointestinal digestion in human beings and the resultant HPH was separated by membrane ultrafiltration into peptide fractions with different sizes (<1 and 1–3 kDa). Their data demonstrated that the peptides act synergistically to produce more effective renin inhibition when present together in the HPH hydrolysate and fractionation of the peptides resulted in the reduction of renin and ACE inhibition effect due to loss of this synergistic effect, probably due to size-dependent partitioning of active peptides into different peptide groups (Girgih *et al.,* 2011). Furthermore, scientists do investigate the inhibitory effect of an individual pure peptide by further purification using high performance liquid chromatography (HPLC) or other techniques like column chromatography or reversed phase high performance liquid chromatography (RP-HPLC) (Bleakley *et al.,* 2017). For instance, rapeseed protein hydrolysate produced using alcalase and its HPLC fractions (Table 1) showed strong inhibitions of renin activity (Table 1). Bioassay-guided purification led to isolation of renin inhibitory peptides, which were identified as TF, LY, and RALP as presented in Table 1 (He *et al.,* 2013). These peptides exhibited *in vitro* and *in vivo* renin inhibitory activity. This study also indicated a potential role for arginine in enhancing renin inhibition by peptides, which is consistent with previous findings for pea peptides (Li & Aluko, 2010). *In vivo* studies showed that oral administration of the peptides to hypertensive rats led to reductions in systemic blood pressure (SBP) with LY being the most active (−26 mmHg) followed by RALP (−16 mmHg) while TF had −12 mmHg (He *et al.,* 2013) as outlined in Table 1.

Table 1: Renin-Inhibitory Bioactive Peptides

Bioactive Peptide	Origin	Proteolytic Enzyme	Reference
IR, EF, KF	Pea protein	Alcalase	Li and Aluko, 2010
SVYT,WYT, IPAGV	Hemp seed protein	Pepsin + Pancreatin	Girgih *et al.,* 2014
IFFFL, FFG, WCY	Oat protein	pepsin + Ficin	Bleakley *et al.,* 2017
PFL, FLLA, WWK	Oat protein	pepsin + Ficin	Bleakley *et al.,* 2017
LY, RALP, GHS	Rape seed protein	Alcalase	He *et al.,* 2019
IRLIIVLMPILMA	*Palmaria palmata*	Papain	Li and Aluko, 2010
HR, YR, HF, HLP	Bovine hemoglobin	Papain	Lafarga *et al.,* 2016
SLR	Bovine serum albumin	Papain	Lafarga *et al.,* 2016
YR, SLR	Bovine fibrinogen	Papain	Lafarga *et al.,* 2015
APPH, IIY, PPL, PPG, FFG, IPP, LPP	Bovine and Porcine hemoglobin, collagen and serum albumin	Papain + Pepsin + Thermolysin	Lafarga *et al.,* 2014

G = Glycine; A = Alanine; P = Proline; V = Valine; L = Leucine; I = Isoleucine; M = Methionine; F = Phenylalanine; Y = Tyrosine; K = Lysine; R = Arginine; H = Histidine; S = Serine; T = Threonine; C= Cysteine; N = Asparagine; Q = Glutamine; D = Aspartate; E = Glutamate.

Mechanism of action of renin inhibitory peptides

Renin-inhibitory peptides use different molecular mechanisms to inhibit renin activity. A previous study showed that rapeseed protein-derived peptides could cross Caco-2 intestinal cell monolayer (Fig. 3), intact and inhibit ACE and renin enzymatic activities (Yang *et al.,* 2017). Also, the peptides significantly inhibited renin mRNA and renin protein production (Fig. 3). Moreover, *in vivo* evaluation of renin-inhibitory effect of pea protein hydrolysate indicated that it inhibited renal renin mRNA expression by about 50% in rats (Li *et al.,* 2011) while egg protein-derived peptide, RVPSL (Table 1), also decreased kidney renin mRNA expression (Yu *et al.,* 2014). Furthermore, a protein hydrolysate was reported to exhibit *in vivo* renin-inhibitory effect via reduction of plasma renin mRNA expression thereby ameliorating hypertension (Li *et al.,* 2011). Likewise the net cationic charge of amino acids in the peptide sequences facilitates peptide-dependent inhibition of renin activity (Aluko, 2019). Digestion of flaxseed protein hydrolysate produced fragments which showed potential renin inhibitory effect (Udenigwe *et al.,* 2009) while enzymatic hydrolysis of pea protein using alcalase generated crude peptide which upon further purification by solid phase extraction (SPE) and reversed phase-HPLC produced renin inhibitory peptides, IR, EF and KF (Li & Aluko, 2010) as shown in Table 1. The renin inhibitory effect exhibited by peptides (Table 1) may be attributed to the cationic property of the amino acids in the sequence owing to the fact that IR and KF each have positively charged amino acid residues compared to EF with negatively charged amino acids. Thus, the findings indicated that IR and KF showed stronger renin inhibitory activity than EF (Li & Aluko, 2010). Moreover, the molecular weight, location and nature of amino acid residues in the peptide sequence contributed a lot to its renin inhibitory effect (Udenigwe *et al.,* 2012). For instance, the presence of low molecular-weight hydrophobic amino acid residues at the N-terminal and high molecular weights amino acid residues at the C-terminal of bioactive peptides can enhance renin inhibition probably due to resistant to digestion by endogenous proteases and are easily absorbed in the intestine as they can easily cross the intestinal barrier and thus exhibited more potency (Udenigwe *et al.,* 2012; Robert *et al.,* 1999). In addition, study on the pattern of renin inhibitory peptides indicated the existence of an interaction between the peptides and the amino acid residues present in the active site of the renin enzyme (Onuh *et al.,* 2015). For instance, renin inhibition kinetics revealed that peptides obtained from chicken skin hydrolysate inhibited renin activity by mixed-type inhibition mechanism, indicating that the peptides can bind to either active site or enzyme-substrate (ES) complex (Onuh *et al.,* 2015). The kinetic analysis of hemp seed proteins hydrolysates also showed a mixed-type inhibitory pattern for the peptide fractions which also revealed that the peptides were not bound only to the active site of renin enzyme but also at the enzyme substrate (ES) complex (Girgih *et al.,* 2011). The results obtained imply that electrostatic charge interactions may play a significant role in determining peptide interactions with renin active site because cationic peptides have lower affinity for amino acid residues in the renin active site when compared non-cationic peptides because bioactive peptides containing amino acids with ionizable side chains such as Asp, Glu, His, Lys, and Arg, impart important functional properties and modulation of the charges on these peptides by pH and may result in significant changes in the bioactivity of these peptides due to denaturation (Girgih *et al.,* 2011; Zhou and Pang, 2018). It is also important to note that a single peptide may exhibit an inhibitory pattern different from that observed using hydrolysates or fractions due to the presence of interfering peptides working together as inhibitors. For example, three potent renin-inhibitory peptides SVYT, WYT and IPAGV were isolated from hemp seed protein hydrolysate inhibited renin enzyme through uncompetitive inhibition mechanism Girgih *et al.,* 2014), while molecular

docking analysis showed the existence of interactions between these peptides amino acid residues present in the active site of the enzyme (Girgih *et al.,* 2014).
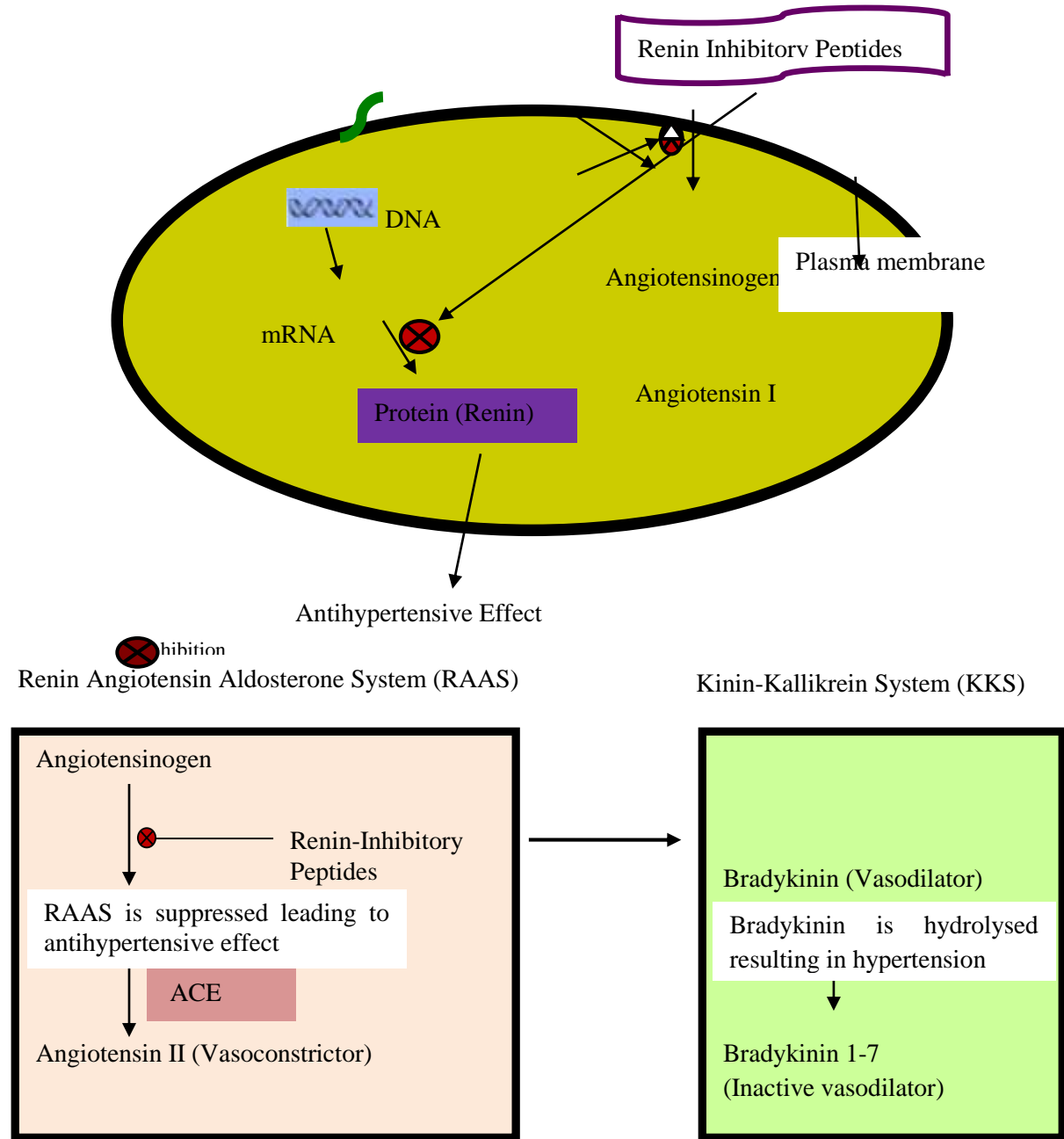

Figure 4: ACE uses KKS as an alternative pathway to activate hypertension

⊗ = Inhibition
▲ = Catalysis

Limitations of Renin Inhibitory Peptides

Since renin-catalyzed conversion of angiotensinogen to angiotensin I is the rate-limiting step of the RAAS pathway, this makes renin a better target than ACE for management of hypertension. However, ACE is a multifunctional enzyme that catalyzes the hydrolysis of bradykinin; a vasodilator to its

inactive form, bradykinin 1-7 via the kinin-kallikrein system (KKS) (Imig, 2004), thereby promoting vasoconstriction and possibly hypertension. Therefore, KKS is an alternative pathway through which ACE can activates hypertension besides RAAS. This indicates that suppressing the RAAS pathway by inhibiting renin is not adequate at preventing hypertension. This limitation could possibly be overcome by co-administration of renin inhibitors and ACE inhibitors or developing a bioactive peptide with inherent potential to inhibit both renin and ACE enzymatic activities. Bioavailability is another challenge in the use of renin inhibitory peptides. For instance, the degree of enzymatic hydrolysis or microbial fermentation of protein is an important factor worth considering since continuous and uncontrolled enzymatic hydrolysis may result in a decrease or loss of bioactivity of the peptides (Daliri *et al.,* 2017), and hence it is important to standardized and /or optimized the degree of enzymatic hydrolysis for each enzyme involved in the enzymatic hydrolysis (Agyei *et al.,* 2016). Therefore, it is difficult to maintain the structure and integrity of bioactive peptide since they lose their stability after oral administration and therefore may not reach the target organs, tissues or cells in therapeutically effective forms (Hernández-Ledesma *et al.,* 2014). Also bioactive peptides are easily degraded in the gut and therefore do not exhibit significant activity in the body when tested *in vivo*. This perhaps is a major challenge and setback in production and commercialization of bioactive peptides. However, this challenge can be overcome by using recombinant DNA technology or genetic engineering approaches to protects the peptides from digestion by endogenous proteases, thereby improving their bioavailability after oral administration (Kaspar and Reichert, 2013; Daliri *et al.,* 2017).

CONCLUSION

Hypertension has been implicated as one of the major risk factor for cardiovascular disease (CVDs) and is amongst the leading cause of death worldwide. Renin catalyzes the rate-limiting step of the RAAS pathway which is crucial in the regulation of blood pressure. Perhaps, this activity makes renin a better target for management of hypertension than ACE. In this review, we highlighted the potential role of renin-inhibitory peptides towards ameliorating hypertension via RAAS pathway. Also this review demonstrated some limitations of renin inhibitors as sole therapy for management of hypertension and therefore, advocates the importance of adopting co-administration of both ACE and renin enzyme inhibitors as the most effective blood pressure control measure than individual alone.

Conflict of interests

The authors declare that they have no conflict of interest associated with this publication and there was no significant financial support for this work that could have influenced its outcome.

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