Review Paper

Food Derived bioactive peptides for Health Enhancement and Management of Some Chronic Diseases

Abstract

The bioactive peptides produced by enzymatic hydrolysis, acid hydrolysis and fermentation approach have been identified and used in enhancement or prevention and management of chronic diseases that are ravaging the world such as T2D, hypertension, oxidative stress, cancer, and obesity . Sources of bioactive peptides have been established ranging from plant to animal and marine foods that has pharmacological effects however depends on target cells and peptides structure and conformations. Plants such as hemp and animal source such as milk among others validate the findings of in vitro and in-vivo studies and the efficiency of these bioactive peptides. This article reviews the literature on BAPs with concerns on food sources, production and BAPS application in enhancement of health and management of hypertension, diabetes and oxidative stress. However, future research efforts on bioactive peptides should be directed towards elucidating specific sequenced bioactive peptides and their molecular mechanisms, through in-vivo and in-vitro studies for specific health conditions in human using nutrigenomics and peptideomic approaches.

Keywords; Food, bioactive peptides, Health, management, hypertension, oxidative stress, diabetes

Introduction.

The human system is subjected to physiological imbalance arising from entropy of the environment allowing extraneous toxic substances that burges normal human system and functions, leading to various health situations. Some artificial contaminants absorbed in protein and lipids from bioaccumulation in plant or animal proteins sources can also raise health risks and cause some chronic diseases such as cancer. Such aberration could be controlled by physiological hemostasis (Chubuike et al,. 2012) as well as health promoting agents (Ames et al,. 1993)

The World Health Organization (WHO) reported about 36 million deaths, resulting from non-communicable diseases, including cardiovascular diseases, diabetes, cancers and chronic respiratory diseases (WHO, 2011).Over the decades, there has been research on bioactive protein hydrolysates and peptides derived from food, which had displayed broad scope of functions but less potent in their effects than synthetic pharmaceutical drugs (Mine et al,. 2010) .Nutrients and non-nutrient portions of food have been used to combat some of the physiological imbalance for decade with less or no improvements on chronic diseases except maintaining health status. This situation has emerged functional foods and nutraceuticals (Molecular nutrition) as an approach to prevention and management of human physiological imbalance or disease at gradual incremental intake maintaining optimal health (Kris Etherton, 2002) .Dietary proteins exert much functionality in vivo by means of biologically active peptides. Such peptides are inactive within the sequence of the parent protein and which are sometimes released by digestive enzymes during gastrointestinal transit or by fermentation or ripening during food processing.

Bioactive peptides are usually encrypted in the amino acid sequences of food proteins (Korhonen and Pihlanto, 2003). Peptides have been defined as specific protein fragments that have a positive impact on body functions or conditions and may ultimately influence health (Kitts and Weiler, 2003;Girgih 2013). These bioactive compounds are molecules or compounds which are active in living organisms, cells or tissues. They contain different kinds of essential molecules which may cure different kinds of diseases of living cells as well, supply proper nutrition to the living organisms (Kepiniski et al,. 2006; Girgih et al,. 2013). Peptides from hemp seed, chicken skin,soy whey and casein proteins has been elucidated by enzymatic hydrolysis as a patent antioxidants and antihypertensive agents (Girgih et al,.2013; Onuh, 2013).Its peptide structure, antioxidant as well as ACE and renin inhibitory actions has been established in vivo and in vitro, hence a potential pharmaceutical products for health enhancement (Girgih et al,. 2013). BAPS from milks has been established to regulate Alpha-glucosidase and dipeptidyl peptidase IV (DPP-IV) enzymes in T2D via satiety response, regulation of incretin hormones and these have been found to reduce the activity of carbohydrate degrading digestive enzymes.(Prasad et al,.2015; Power etal,.2014).Similarly, peptides from skin gelatin, against DPP-IV inhibition had also been established (Patil and others 2015). Atlantic salmon skin gelatin was found to be a potent material exerting the DPP-IV-inhibiting effect. This effect was confirmed in both hydrolysates produced with different proteases as well as peptides fractionated by ultrafiltration.

BAP have been captured by food processors, genomic engineers and the industries, and had identified production of bioactive peptides from plant and animal sources. These active bioactive peptides have potential pharmaceutical properties beyond adequate nutrition. Applications of bioactive peptides are gaining attention at different areas such as supplementation, fortification, proteomic and peptideomic studies. Derived peptides play critical role in human living cells. From dietary point of view, peptides are more bioavailable than proteins or free amino acids (Shimuzu et al,. 2005).They have less side effect than pharmaceutical drugs, hence potential alternative to pharmaceutical drugs

The review seeks to elucidate bioactive peptides and their mechanisms of actions originating from plant and animal food sources that exhibit bio activities typical of enhancing and management of chronic disease such as hypertension, diabetic and oxidative stress.

THE FOOD SOURCE OF BIOACTIVE PEPTIDES

Food protein sources for BAPS come from animal and plant .Food protein from plants includes soybean, legumes, pea's hempseed, pulse, oat wheat conola and flaxseed. BAPS could also come from waste food materials. Food protein bioactive peptides from animal sources includes milk, (casein and whey), egg,meat muscle, caterpillars, termites. Marine sources includes; salmon, oysters, jelly fish, (Chuibuike et a,.2012 ; Girgih et al,.2011).Peptide fractions from food sources have been established, IPP and VPP from milk (Mizushima et al., 2004); ESIINF and IVF fractions from egg (Miguel et al ,.2007; Miguel et al,. 2005); IKW and LKP from chicken muscles (Fujita et al ,. 2000); VKKVLGNP and KRQKYDI. Plant sources of bioactive peptides are numerous including DLP and DG from soy proteins (Wu and Ding, 2001; Wu and Ding, 2002); LQP and IQP from wheat bran (Nogata et al,. 2011); KF and EF from pea (Li and Aluko, 2010); LY and RALP from rapeseed (He et al., 2013); VF and KY from Wakame (Suetsuna et al,. 2004); LRP and LSP from maize (Puchalska et al,. 2013); KDYRL and VTPALR from mung bean (Li et al,. 2006); WNI, LNA, QGR and RW from flaxseed (Marambe et al,. 2011; Udenigwe et al., 2012); EVPK and VVGAK fractions from sweet potato (Huang et al., 2011) as

well as from mushroom and pumpkin, most of this fractions have multi-functional properties for health enhancement.(Table 1.)

According to (Chuibuike et al,.2012, Girgih 2011) choice of bioactive peptides food sources are based on value addition from underutilized rich protein sources and the utilization of specific amino acid for particular medical formulation. Recently a Nano based approach have been proposed to predict protein sources (Gu et al ,.2011), which could lead to excellent selection of rich food protein sources for bioactive peptides production.

Table 1; **BAPS from plant origins**

Protein	Enzyme	Peptides /Function /Sequence	Health Effect	Reference
Plant source;				
Hemp seed.	Proteolytic enzyme	Inhibit ACE	Anti- hypertensive	Girgih et al,. 2011
Pea seed	Alcalase	InhibitACE (IR,KFand EF)	Anti- hypertensive	Huan et al,. 2010
Soyabean.	Enymatic Hydrolysis	Anti- hypocholesterol (Leu-pro-try-pro)	cholesterol reduction	Zhang et al,. 2007
Wheat glutein	Aspergillus Oryzae Protease. Hydrolylate and fractions	Pyrolglutamyl leucine	Anti – inflammatory and mucosal Improvement	Sato etal ,. 2013
Black bean	Enzymatic hydrolysis	Inhibit glucose transport (AKSPLF,ATNPLE FEELN, LSVSVL)	Reduce blood pressure	Chakraor et al,. 2014

Table 2:BAPS from animal origins

Protein	Enzyme	Peptides /Function /Sequence	Health Effect	Reference
Animal source:				
Oyester	Protease soln from Bacillus spp	Anti -tumor (peptide <3Kda)	Multi-functional ppty	Wang et al,. 2010
Jelly fish Collagen	protamex	D-glucose induced aging	Anti- oxidant	Ding et al,. 2011
Salmon	protease	Immune booster	multifunctional Immune stimulation	Yanget al,. 2010
Insect) (silkworm)	Enzyme hydrolysis Acid hydrolysis	High inhibitory activity on ACE	ACE inhibitory drugs	Wang et al,. 2008 Cito et al,. 2017
Chicken Skin	Acalase	Inhibitory on ACE Protein Kda <1,1-3,3-5,5-10)	InhibitACE scavenging activity	Onuh,2015
Crabs	protamex	Cancer Inhibition	Anti- tumor	Doyen et al ,. 2011
Shrimp shell By products enzyme	Cryotin	Cancer Inhibition	Anti –Cancer	Kannon etal,. 2011

Production of Bioactive Peptides

Research of recent years has shown that dietary proteins provide a rich source of biologically active peptides. Bioactive peptides are produced from precursor proteins where they occur as inactive amino acid sequences but can be released using the following methods:

(a) enzymatic hydrolysis by digestive enzymes,

(b) fermentation of precursor proteins with proteolytic starter cultures and

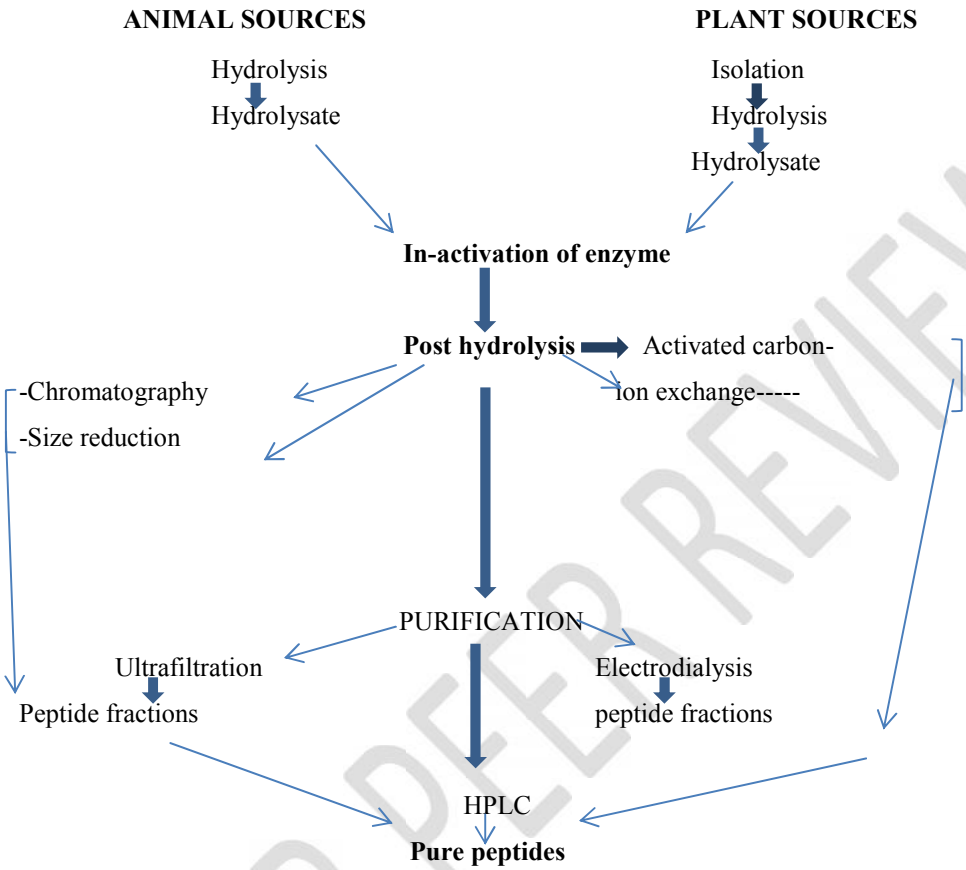
(c) proteolysis by enzymes derived from microorganisms or plants (Korhonen & Pihlanto, 2007).

The activity of peptides is based on their inherent amino acid composition and sequence and their size could range from 2 to 20 amino acid residues.

The production and processing of bioactive peptides from animal source and plant varies. The production of baps from animal source require hydrolysis as the major stage, however plant

source of baps require isolation and hydrolysis, this two major stages in plant baps may be due to attached side chain moieties in plant tissues.

Fig 1:



Bioactive peptides are attached on the primary structure of plant and animal cells as an in active amino acid sequence which can be released by fermentation, enzymatic hydrolysis, and acid hydrolysis and via food processing. These methods of releasing the primary amino acid could be done in-vivo or in-vitro (Aluko, 2008). The release of these bio actives hydrolysate and peptides have shown a better bioactivity than parent protein across enterocytes or intestinal walls and to target cells (Chuibuke et al ,.2012;Girgih et al,.2011).

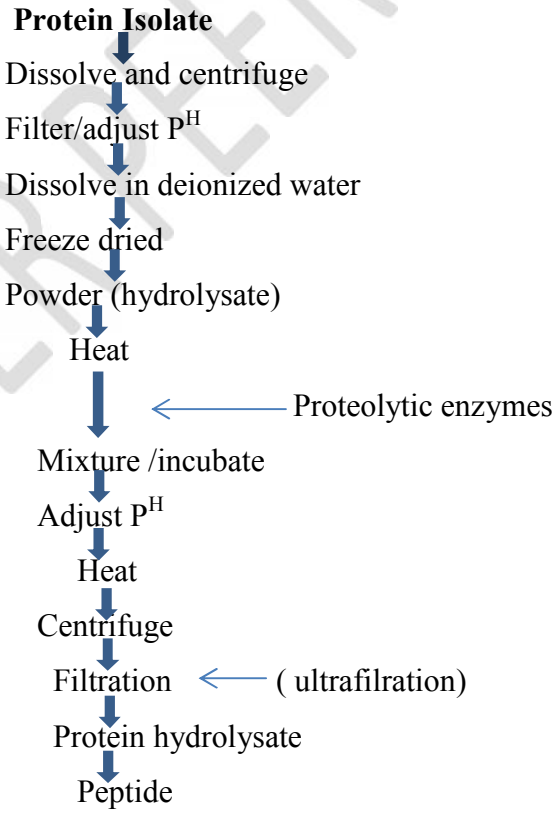
The major and common method of PABS production is by enzymatic hydrolysis, acid and fermentation methods. Peptides could be released from food source hydrolytically using single, multiple or specific or non -specific mimic digestive proteases. This approached has been established in-vitro and in-vivo (Chubuike at al ,.2012 Girgih et al,. 2011 ;Onuh, 2012).The release of peptides by this approached are factored by enzyme selection, hydrolysis time degree of

hydrolysis substrate enzyme ration and pretreatments (Chubuike at al ,.2012 Girgih et al,. 2011) .Sonication, Thermal treatment , hydrostatic pressure can increase enzyme protein interactions(Inouge et al,. 2009.Quiro et al,. 2007; Wu and Mgunder, 2009).

Enzymatic Hydrolysis of Peptides.

Enzymatic hydrolysis has been the common way of producing bioactive peptide with trypsin activity on ACE inhibition (Marayama et al ,. 1982. Berrocal et al ,. 1989). Other enzymes and their combination for bioactive peptide include proteolytic enzyme (Alcalase , chymotrypsin, pancreatin and pepsin).However, more than a single proteolytic enzyme can be used for hydrolysis in peptide formation via stepwise or simultaneous approaches .See (fig 2). The formation of peptide using this approach is a function of P^H, Temperature and Time. (Sangsawad et al,. 2007). There are no established peptide products of food from a proteolytic enzyme but chain length and molecular weight determine peptide functionality.(Zhang et al,. 2017 ; Hauang et al ,.2017). Low molecular weight peptides (<10ka) have been found more effective against oxidative stress and hypertension.(Girgih et al 2011;Onuh,2013).

Fig 2

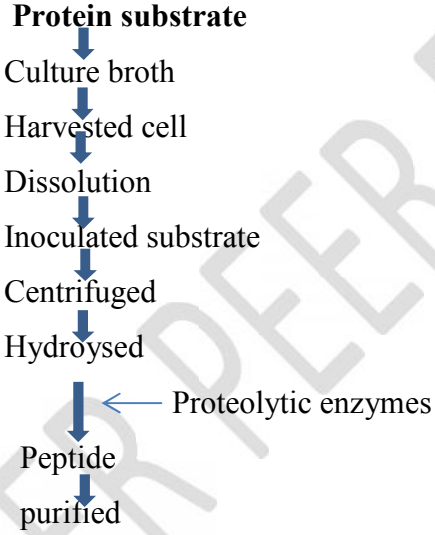


Adopted by (Tang et al,. 2006)

Microbial Fermentation

Fermentation using microorganism for bioactive peptide production involves the use of selective or combined strains of yeast, bacterial or fungi to make culture which PH and temperature dependent. During microbial fermentation harvesting, increasing surface area before hydrolysis depends on strain of microorganism used, protein source and fermentation time. Fig 3(Eric et al ,.2017 Ahn et al ,.2009).Bioactive peptides from whey fermented by lactobaccilus brevies had strong inhibitory ACE ability than other lactobacillus strains.This strain selectivity was observed by(Matar et al,. 2003;fitzgerald and Murrey , 2006,Gobbetti et al,. 2007).Yoghurt and cheese starter and probiotic have been discovered to produce bioactive peptide in milk during fermentation Gomez ruizeetal,. 2002 ;Dankor et al,. 2007)

Fig 3



Bioactive Peptides in the prevention and Management of Hypertension.

Studies conducted to evaluate the antihypertensive potentials of food derived peptides from natural foods of plant and animal origin and the ability of these peptides to prevent or treat hypertension have been carried out *in vitro* (Hernández-Ledesma et al,.2011; Jauhiainen & Korpela, 2007; Murray and Fitzgerald, 2007). The potential antihypertensive effect of a peptide depends structurally on intactness and active form, resistance to cleavage by digestive proteinases and peptidases, and transportation through the brush border membrane without loss of integrity(Girgih et al,.2011).Although, the blood pressure lowering effect of most bioactive peptides is less than that of pharmaceutical drugs, the negative side effects associated with the

long-term use of antihypertensive drugs is causing a gradual shift of attention to natural food protein-derived peptides.

Natural food protein-derived peptides with potent ACE-inhibitory activity have attracted much attention and a large number of these peptides that exhibit various amino acid sequences have been isolated and characterized from enzymatic hydrolysates of foods, such as grass carp fish, oysters, gelatin, egg, milk, whey peptides (Hernández-Ledesma et al,. 2011; Zhang et al,. 2009)) Chicken peas and yellow peas using Alcalese and papain hydrolysates has been reported to inhibited ACE in-vitrol (Barbana et al,. 2010) .Eggs using thermolysin and alcalase was also reported to effect ACE inhibitory activity (You et al ,.2011) Animal protein peptides from pork meat has been established via oral administration of its fractions RPR,KKAPVA,PTPVP with RPR fractions exerting more ACE inhibitory vivo activity (Escudero et al ,.2012).

The renin-angiotensin-aldosterone system (RAAS) plays a major role in the regulation of blood pressure and normal heart function (Figure 4). Renin is an aspartyl protease that catalyzes the conversion of angiotensinogen to angiotensin I (AT I) (Erdmann et al., 2007; Nagpal et al., 2010, Phelan et al,. 2011). Subsequently, ACE (a peptidyldipeptide hydrolase, EC 3.4.15.1) catalyzes the conversion of AT I to angiotensin II (AT II) leading to constriction of the blood vessels, hence an increase in blood pressure .ACE also inactivates the activity of the potent vasodilator, bradykinin 6 and subsequently results in an increase in blood pressure (Erdmann et al., 2007). Thus, the inhibition of ACE is a crucial target for antihypertensive activity.

The mechanism involved in modulating the renin-angiotensin system (RAS) that controls blood pressure is critical for the prevention or treatment of hypertension .ACE alone does not completely prevent production of Angiotensin II, the vasoconstrictor which is continually produced from an ACE independent pathway catalyzed by chymase (Fig. 4). The most studied BP control pathways with regard to food-derived peptides involve those shown to inhibit ACE and renin enzymes *in vitro*. These enzymes are the main regulators of BP and are both involved in the renin-angiotensin system (RAS), in addition ACE is also involved in the kinin-nitricoxide system (KNOS). Inhibition of ACE and renin in these systems leads to relaxation of the artery walls (vasodilation) and subsequent lowering of BP.

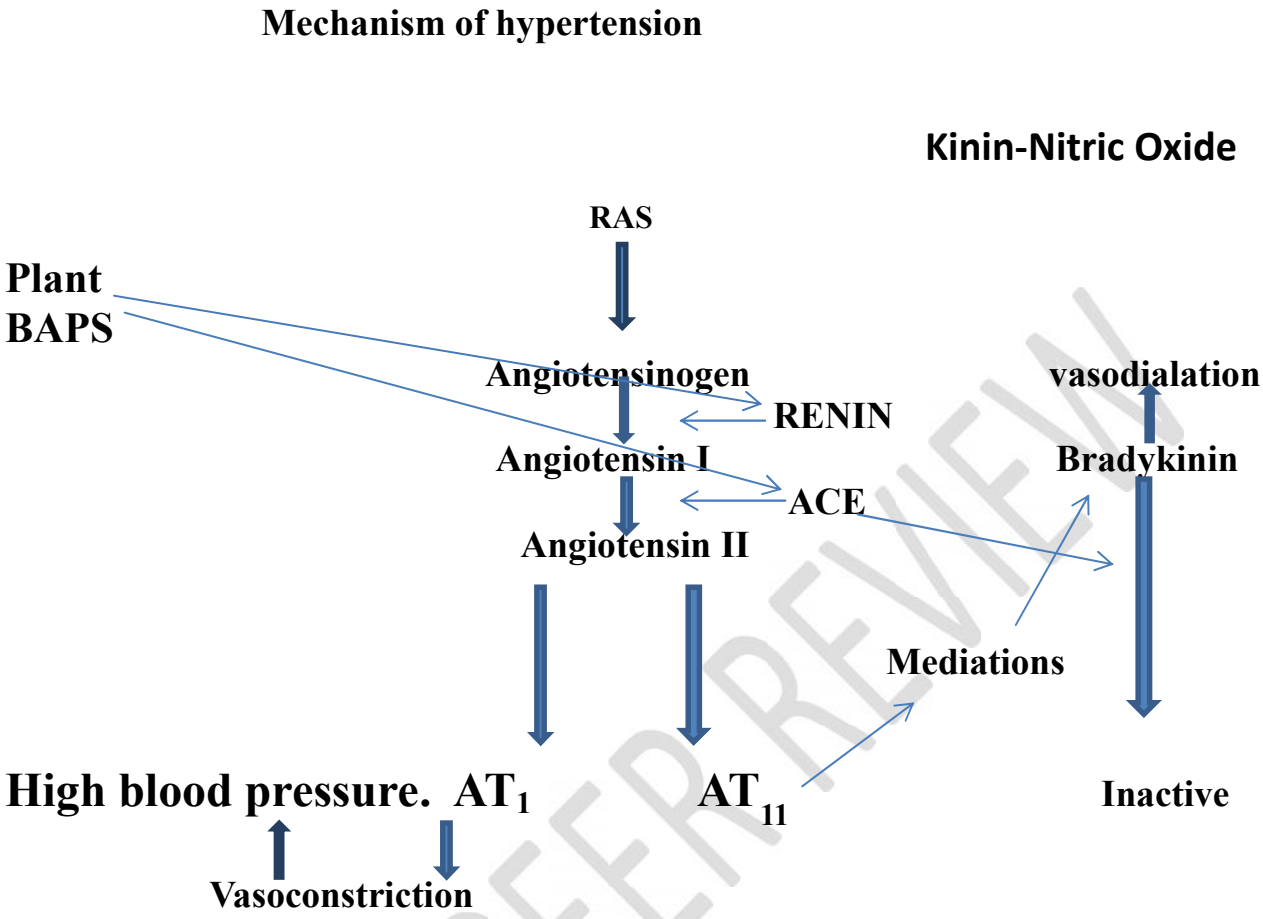


Fig 4; Mechanism and Intervention on hypertension by bioactive peptides.

(Adopted from Girgih et al ,.2013)

Bioactive Peptides in the Management of Oxidative Stress (anti – oxidants)

Oxidative stress occurs as a result of imbalance between the production of free radicals, reactive oxygen species (ROS) and the scavenging ability of endogenous ant-oxidants. Excessive production of ROS may damage membranes, proteins, enzymes and DNA resulting in the development of chronic disease conditions (Girgih et al ,.2011; Bidlingmeyer et al,.1984) Enzymatic food protein-derived peptides, in comparison to synthetic compounds are believed to be safer natural antioxidants that can be used as protective agents to help the human body reduce oxidative damage and associated diseases (Girgih et al,.2011) . The antioxidant properties o bioactive peptides, hydrolysates largely depend on enzyme specificity, degree of hydrolysis and the nature of the peptides released including molecular weight, amino acid composition and hydrophobicity Gehrke et al,.1985; You et al,.2010) . The antioxidant properties of peptides include their ability to scavenge free radicals, inhibit linoleic acid autoxidation, act as chelating

agents of metal ions, or as reducing agents (Tang et al,.2009) . The presence of certain amino acids like, histidine, tyrosine, methionine, lysine, tryptophan and proline increases the antioxidant potency of most food-derived peptides (Aluko and Monu , 2003) . It was found that overall, alcalase and proteinase-k were more efficient proteases in releasing bioactive peptides from rapeseed with potent antioxidant properties compared to combined pepsin + pancreatin, flavourzyme and thermolysin (He et al,. 2013). Several other natural antioxidant peptides have been produced from soy proteins, sunflower, pea, chickpea, flaxseed, salmon, shark liver, beef, fish skin, milk and chicken bone. Studies have shown peptides with antioxidant property released from food sources, including cow's milk (Kumar et al., 2011), eggs (Chen et al., 2011), soy protein (Amadou et al., 2011), fish (Bougaterf et al,. 2009, Najafian et al,. 2011), wheat (Koo et al,. 2011), marine rotifer (Byun et al,. 2009), chickpeas (Yust et al,. 2011) and African yam bean (Ajibola et al,. 2011).

Several diseases have been proposed to be mediated by radical or oxidant species, it is valuable to learn about these antioxidant compounds that might block, inhibit, or prevent radical-initiated reactions as well as elucidate the mechanisms of their action (Krinsky, 1992). Knowledge of the various mechanisms by which bioactive peptides are able to achieve their roles as antioxidants in the prevention of oxidative stress related ailments abounds but specific tailored peptide sequences of desired amino acid composition with the potential to scavenge, reduce ROS/RNS/free radicals and chelate transition metals as well as act as lipid peroxidation agents are critical (Girgih et al,.2013).

However, several mechanisms of antioxidant action of food derived bioactive peptides against ROS/RNS and free radicals have been proposed (Dai and Mumper, 2010). These include: radical scavenging species such as ROS/RNS and free radicals by readily donating hydrogen atoms or electrons to quench their destructive effects on biomolecules, via peptide bonds and hydroxyl substituents. Secondly, by suppression of ROS/RNS and free radical formation via inhibition of certain pro-oxidant enzymes and chelating of transition metal ions that are involved in catalyzing free radical production. Thirdly, by upregulating the function of the antioxidant enzyme-linked defence mediated by endogenous antioxidants such as reduced glutathione (GSH), ascorbate, superoxide dismutase and catalase (Duthie et al., 2006) or enzyme modulation of cellular physiological and biochemical reactions (Vattem et al,. 2005). Fig. 5 illustrates the initiation of ROS/free radical production, their destructive effects on cellular organelles leading to the

development of chronic diseases and the use of bioactive peptides as an intervention strategy. The initiating species for the production of ROS/free radicals is superoxide radical which is converted to hydrogen peroxide that could be broken down into harmless metabolites such as water and oxygen in the presence of endogenous antioxidants including superoxide dismutase, catalase, glutathione etc. In disease state, excessive ROS/free radicals are produced and the body's natural mechanism to inactivate them is overwhelmed resulting in the conversion of hydrogen peroxide to the most toxic radical called hydroxyl radical. This reaction is catalyzed by transition metals (Cu^{2+} and Fe^{2+}). If the situation is not attended to, the harmful radicals begin to damage tissues, cell membranes, proteins, enzymes, and DNA, which leads to the progression of chronic diseases such as diabetes, cancer, obesity and can cause adverse cardiovascular events.

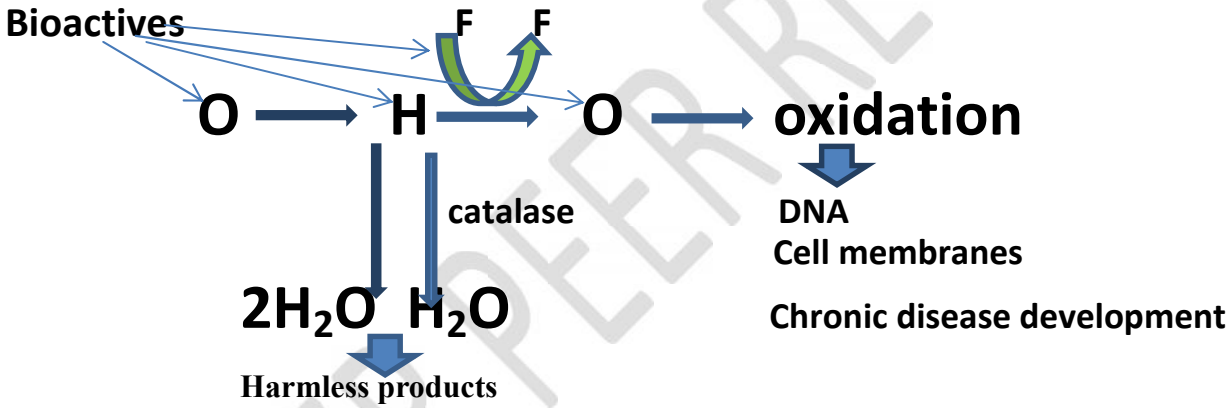


Fig 5; possible mechanisms of action of bioactive peptides in oxidative condition (**Adapted from Young and Woodside, 2001)**

Bioactive Peptides in Diabetic Prevention and Management

Diabetes mellitus (DM), a chronic metabolic disorder caused by defective insulin production characterized by hyperglycemia, a condition in which surplus of sugar is present in the blood stream. Prevalence of diabetes mellitus is increasing markedly because of aging, population growth, increasing urbanization, incidences of obesity, and more sedentary lifestyles. Type 1 diabetes (T1D) and Type 2 diabetes (T2D) are the main two types of diabetes. Though the latter is much more common and accounts for 90-95 % of all diabetes. A number of factors, such as insulin resistance, hyper insu-linemia, impaired insulin secretion, reduced insulin mediated glucose uptake, and utilization convoluted the treatment of T2D (Fig. 6). The regulation of

Alpha-glucosidase and dipeptidyl peptidase IV (DPP-IV) enzymes in T2D via satiety response, regulation of incretin hormones regulations are the mechanism to reduce the activity of carbohydrate degrading digestive enzymes.(Prasad et al,.2015; Power etal,.2014).Skin gelatin against DPP-IV inhibition had been established (Patiland others 2015). Atlantic salmon skin gelatin was found to be a potent material exerting the DPP-IV-inhibiting effect. This effect was confirmed in both hydrolysates produced with different proteases as well as peptides fractionated by ultrafiltration.

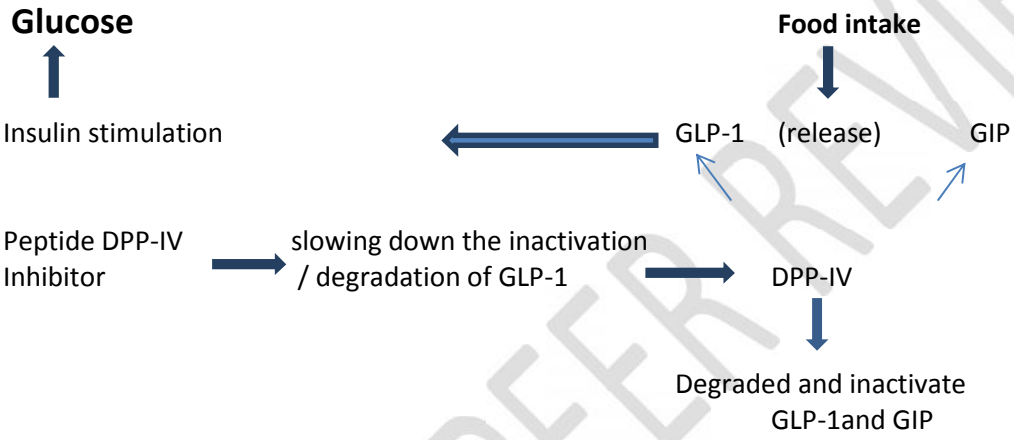


Fig 6 ;Glucose mediation mechanism by bioactive peptides

CONCLUSION

This review has shown that peptides derived through enzymatic, acidic and fermentation of plant and animal food protein hydrolysates possesses bioactive materials that could on an incremental bases stops the rate of cell damage that could arise from oxidative stress, enzymatic synthesis (Renin agniostesen system RAS) hence management and prevention of hypertension, diabetes and oxidative stress which are relevant to the sustenance of human health and physiological stability. This area is growing with the discovery of new molecular nutrients for molecular disease management. With a lot of information existing on the various bioactivities of food protein-derived peptides, hence research should be directed toward evaluation of specific sequenced

418 peptides from varied sources in the management and prevention of some chronic disease
419 peptideomically, its bioavailability, and for making specific functional foods and pharmaceutical
420 drugs.
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