Food Derived Bioactive Peptides for Health Enhancement and Management of Some Chronic Diseases

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ABSTRACT

The bioactive peptides produced by enzymatic hydrolysis, acid hydrolysis and fermentation approach have been identified and used widely in research. These methods are important in enhancement or prevention and management of chronic diseases that are ravaging the world such as type -2-diabetes, hypertension, oxidative stress, cancer, and obesity. Sources of bioactive peptides have been established ranging from plant to animal and marine foods that have pharmacological effects; however these effects are dependent 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 in the management of certain chronic diseases. This article reviews the literature on bioactive peptides with concern on food sources, production and bioactive peptides application in...
enforcement of health and management of hypertension, diabetes and oxidative stress. Future research efforts on bioactive peptides should be directed towards elucidating specific sequenced bioactive peptides and their molecular mechanisms, through \textit{in-vivo} and \textit{in-vitro} studies for specific health condition in human using nutrigenomics and peptidomic approaches.

\textbf{Keywords:} Food; bioactive peptides; health and management; diseases.

\section*{1. INTRODUCTION}

The human system is subjected to physiological imbalance arising from entropy of the environment allowing extraneous toxic substances that disturbed normal human systems and functions, leading to various health conditions. Some artificial contaminants absorbed in protein and lipids from bioaccumulations 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 \cite{1} as well as health promoting agents \cite{2}.

The World Health Organization (WHO) reported about 36 million deaths, resulting from non-communicable diseases, including cardiovascular diseases, diabetes, cancers and chronic respiratory diseases \cite{1}. 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. 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. Dietary proteins exert much functionality \textit{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 \cite{3}. Peptides have been defined as specific protein fragments that have a positive impact on body functions or conditions and may ultimately influence health \cite{9}. 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 in living cells as well, supply proper nutrition to the living organisms \cite{4}. Peptides from hemp seed, chicken skin, soy whey and casein proteins has been elucidated by enzymatic hydrolysis as a patent antioxidants and antihypertensive agents \cite{5,6}. Its peptide structure, antioxidant as well as ACE and renin inhibitory actions has been established \textit{in vivo} and in vitro, hence a potential pharmaceutical products for health enhancement \cite{4}. Bioactive peptides from milks has been established to regulate Alpha-glucosidase and dipeptidyl peptidase IV (DPP-IV) enzymes in type 2 diabetes via satiety response, regulation of incretin hormones and these have been found to reduce the activity of carbohydrate degrading digestive enzymes \cite{7}. Similarly, peptides from skin gelatin, against DPP-IV inhibition had also been established \cite{8}. 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.

Bioactive peptides have been captured by food processors, genomic engineers and the industries, and have 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 peptidomic 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 \cite{9}. 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.
2. THE FOOD SOURCE OF BIOACTIVE PEPTIDES

Food protein source for bioactive peptides 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, [10,11]. Peptide fractions from food sources have been established, such milk, peptides fractions as IPP and VPP from milk [12]; Peptides fractions like ESINIF and IVF from egg; IKW and LKP fractions from chicken muscles [13] Plant sources of bioactive peptides are numerous including DLP and DG peptides fractions from soy protein [7,1] LQP and IQP peptides fractions from wheat bran [14]; KF and EF peptides fractions from pea [15]; LY and RALP peptides fractions from rapeseed; VF and KY peptides fractions from Wakame [9]; LRP and LSP peptides fractions from maize [16]; KDYRL and VTPALR peptide fractions from mung bean [13]; WNI, LNA, QGR and RW peptide fractions from flaxseed [13,12]; EVPK and VVGA fractions from sweet potato [17] as well as from mushroom and pumpkin, most of this fractions have multi-functional properties for health enhancement (Tables 1 and 2).

According to many researchers [1] and [18] 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 (Tables 1 and 2). Recently a Nano based approach have been proposed to predict protein sources , which could lead to excellent selection of rich food protein sources for bioactive peptides production.

3. 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 [12].

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 (Tables 1 and 2). The production of bioactive peptides from animal source (Fig. 1) require hydrolysis as the major stage, however plant source of bioactive peptides (Fig. 1) 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 [19]. The release of these bio actives hydrolysate and peptides has shown a better bioactivity than parent protein across enterocytes or intestinal walls and to target cells [1,18].

The major and common method of bioactive peptides 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 approach has been established in-vitro and in-vivo [1,20,21]. The release of peptides by this approach are factored by enzyme selection, hydrolysis time degree of hydrolysis substrate enzyme ration and pretreatments [22,23]. Sonication, Thermal treatment, hydrostatic pressure can increase enzyme protein interactions [24,7].

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### Table 1. Bioactive peptides origins

<table>
<thead>
<tr>
<th>Plant source</th>
<th>Enzyme</th>
<th>Peptides /Function/Sequence</th>
<th>Health effect</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemp seed</td>
<td>Proteolytic enzyme</td>
<td>Inhibit ACE</td>
<td>Anti- hypertensive</td>
<td>[18;25]</td>
</tr>
<tr>
<td>Pea seed</td>
<td>Alcalase</td>
<td>Inhibit ACE(IR,KF and EF)</td>
<td>Anti- hypertensive</td>
<td>[20]</td>
</tr>
<tr>
<td>Soyabean.</td>
<td>Enzymatic Hydrolysis</td>
<td>Anti- hypocholesterol Leu-pro-try-pro</td>
<td>cholesterol reduction</td>
<td>[14;26]</td>
</tr>
<tr>
<td>Wheat gluten</td>
<td>Aspergillus Oryzae Protease Hydrolylate</td>
<td>Pyroglutamy leucine</td>
<td>Anti – inflammatory and mucosal Improvement</td>
<td>[1]</td>
</tr>
<tr>
<td>Black bean</td>
<td>Enzymatic hydrolysis</td>
<td>Inhibit glucose transport(AKSPLF,ATNPLE FEELN, LSVSVL peptides fractions)</td>
<td>Reduce blood pressure</td>
<td>[9;27]</td>
</tr>
</tbody>
</table>

### Table 2. Biactive peptides from animal origins

<table>
<thead>
<tr>
<th>Animal source</th>
<th>Enzyme</th>
<th>Peptides /Function/Sequence</th>
<th>Health effect</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oyster</td>
<td>Proteas solution from Bacillus spp</td>
<td>Anti tumor peptide &lt;3Kda</td>
<td>Multi-functional properties</td>
<td>[28]</td>
</tr>
<tr>
<td>Jelly fish collagen</td>
<td>Protamex</td>
<td>D-glucose inducing aging</td>
<td>Anti- oxidant</td>
<td>[29]</td>
</tr>
<tr>
<td>Salmon</td>
<td>Protease</td>
<td>Immune booster</td>
<td>Multifunctional stimulation</td>
<td>[16]</td>
</tr>
<tr>
<td>Insect</td>
<td>Enzyme hydrolysis Acid hydrolysis</td>
<td>High inhibitory</td>
<td>activity on ACE</td>
<td>[28]</td>
</tr>
<tr>
<td>Silk worm</td>
<td>Alcalase</td>
<td>Inhibitory on ACE protein KDa 1,1-3,3-5,5-10</td>
<td>Inhibit ACE scavenging activity</td>
<td>[21]</td>
</tr>
<tr>
<td>Chicken skin</td>
<td>Protamex</td>
<td>Cancer Inhibition</td>
<td>Anti- tumor</td>
<td>[30]</td>
</tr>
<tr>
<td>Shrimp shell By products enzyme</td>
<td>Cryotin</td>
<td>Cancer Inhibition</td>
<td>Anti–Cancer</td>
<td>[31]</td>
</tr>
</tbody>
</table>
4. ENZYMATIC HYDROLYSIS OF PEPTIDES

Enzymatic hydrolysis has been the common way of producing bioactive peptide with trypsin activity on ACE inhibition [14]. 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. (Fig. 2). The formation of peptide using this approach is a function of pH, Temperature and Time [9]. There are no established peptide products of food from a proteolytic enzyme but chain length and molecular weight determine peptide functionality [32,33]. Low molecular weight peptides (<10 kDa) have been found more effective against oxidative stress and hypertension [2,21].
5. 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 as shown in Fig. 3 [34]. Bioactive peptides from whey fermented by *Lactobacillus brevis* had strong inhibitory ACE ability than other lactobacillus strains. This strain selectivity was observed by [5]. Yoghurt and cheese starter and probiotic have been discovered to produce bioactive peptide in milk during fermentation [33].

6. 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 [5,3] The potential antihypertensive effect of a peptide depends structurally on intactness and active form, resistance to cleavage by digestive proteases and peptidases, and transportation through the brush border membrane without loss of integrity [23]. 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 [3,13] Chicken peas and yellow peas using Alcalase and papain hydrolysates has been reported to inhibit ACE *in-vitro* [16]. Eggs using thermolysin and alcalase was also reported to effect ACE inhibitory activity [35] Animal protein peptides from pork meat has been established via oral administration of its fractions RPR, KKPVA, PTPVP with RPR fractions exerting more ACE inhibitory *vivo* activity.

The renin-angiotensin-aldosterone system (RAAS) plays a major role in the regulation of blood pressure and normal heart function (Fig. 4). Renin is an aspartyl protease that catalyzes the conversion of angiotensinogen to angiotensin I (AT I) [32]. Subsequently, ACE (a peptidyl dipeptide 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 . 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.
7. 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 anti-oxidants. Excessive production of ROS may damage membranes, proteins, enzymes and DNA resulting in the development of chronic disease conditions [23]. 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 [23]. The antioxidant properties of 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 [35]. 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 [10]. The presence of certain amino acids
like, histidine, tyrosine, methionine, lysine, tryptophan and proline increases the antioxidant potency of most food-derived peptides [22]. 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, flavoursome and thermolysin [26]. 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 [28], eggs [4], soy protein [24], fish [36] wheat [29], marine rotifer [8], chickpeas [35] and African yam bean [37].

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 [12,13]. 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 [20].

However, several mechanisms of antioxidant action of food derived bioactive peptides against ROS/RNS and free radicals have been proposed [30]. These include the 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 defense mediated by endogenous antioxidants such as reduced glutathione (GSH), ascorbate, superoxide dismutase and catalase (34) or enzyme modulation of cellular physiological and biochemical reactions [38]. 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 (Cu2+ and Fe2+). 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.

8. 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% to 95% of all diabetes. A number of factors, such as insulin resistance, hyper insulinemia, 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 incretion hormones regulations are the mechanism to reduce the activity of carbohydrate degrading digestive enzymes [7]. Skin gelatin against DPP-IV inhibition had been established [16]. 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

9. 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 Angiotensin 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 peptides from varied sources in the management and prevention of some chronic disease peptidomeically, its bioavailability, and for making specific functional foods and pharmaceutical drugs.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

30. Girgih AT, Udenigwe CC, Hasan FM, Gill TA, Aluko RE. Antioxidant properties of salmon (Salmo salar) protein hydrolysate and peptide fractions isolated by reverse-


