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Mini Review

Bioactive Peptides with Antihypertensive Property Obtained from Agroindustrial Byproducts – Mini Review

Lemes AC[1], de Paula LC[2], Filho JGO[3], do Prado DMF[4], Medronha GA[5] and Egea MB[4]*

[1]Department of Biochemical Engineering, Federal University of Rio de Janeiro (UFRJ), School of Chemistry, Av. Athos da Silveira Ramos, Brazil

[2]Department of Food Engineering, Federal University of Rondônia (UNIR), Av Tancredo Neves, Brazil

[3]São Paulo State University (UNESP), School of Pharmaceutical Sciences, Rod Araraquara Jaú, Brazil

[4]Goiano Federal Institute of Education, Science, and Technology, Campus Rio Verde, Brazil

[5]Hospital de Clínicas de Porto Alegre, Programa de Residência Médica em Dermatologia, Rua Ramiro Barcelos, Brazil

***Corresponding author:** Mariana Buranelo Egea, Goiano Federal Institute of Education, Science, and Technology, Campus Rio Verde, Rod. Sul Goiana, Km 01, Cx Postal 66 - Cep: 75901-970, Rio Verde, GO, Brazil

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Abstract

Agroindustrial processes generate large amounts of protein byproducts that can be used as a source of bioactive molecules. Several peptide sequences from these materials have already been shown to be potential antihypertensive agents, acting in the inhibition of the renin–angiotensin–aldosterone system. Therefore, these molecules demonstrate the potential for application in prevention and antihypertensive treatment, reducing cardiovascular complications, especially combined with physical activity and the adoption of a healthy diet.

Keywords: Angiotensin Converting Enzyme; Vasorelaxant; Cardiovascular Diseases; Health

Introduction

The food industry generates large quantities of residues considered a problem due to their environmental impacts [1,2]. Although part of these residues are used in animal feed or even as fertilizers, and therefore known as byproduct or coproducts, this destination is still not sufficient for total use, resulting in inappropriate discards that contribute even more to pollution problems [3,4].

On the other hand, the byproducts generated can contain substances that can demonstrate several health benefits due to their bioactive properties. Thus, the application of suitable processes and technologies can promote the transformation of raw materials with little or no applicability into high-value components, such as peptides [2,5,6].

Bioactive peptides are specific fragments of proteins, which generally contain between 3 and 20 amino acid residues, being able to positively impact the functions or conditions of the body and, thus, influence health [7]. Depending on the composition and sequence of amino acids in the structure of bioactive peptides [8], they can act as potential antihypertensives [9], antimicrobials [10], antioxidants [11,12], antithrombotics [13], and also in the control of diabetes and neurological diseases, such as Alzheimer's [14].

The peptides can be presented in the native form, free to exercise their bioactivities or, still, in an encrypted form, inserted in the native sequence of the proteins. However, they can be released by hydrolysis through the use of specific enzymes or proteolytic microorganisms, and/or by the action of proteases from different sources applied to proteins [5].

The positive effect on health, after ingestion, occurs if the peptides undergo enzymatic hydrolysis and pH change that occur during passage through the gastrointestinal tract. In addition, the peptides must be absorbed and access the specific place of action in the human body, where they will exercise specific physiological functions related to their composition and amino acid sequence [5,15].

Arterial hypertension is a risk factor for several chronic diseases, as well as for the occurrence of metabolic syndrome. Although several pharmaceutical products are available on the market, drug responses show the variability of results and high toxicity in some patients [16]. In addition, with prolonged use, the side effects of conventional drugs tend to manifest themselves in the form of metabolic disorders among patients, such as diabetes, for example [17].

In this sense, bioactive peptides derived from food proteins represent an appropriate group of natural compounds that can serve as potential alternative antihypertensive agents, with lesser side effects [18]. Several studies have already shown that peptide sequences can act in a similar way to conventional drugs used with antihypertensive function, inhibiting the activities of the renin, ACE, and angiotensin II receptors, in vitro and in vivo, in addition to increasing the levels of Nitric Oxide (NO) in the blood [18,19].

Several proteins, of both animal and vegetable source, have been identified as a source of bioactive peptides after hydrolysis processes, including proteins derived from milk, eggs, meat, fish, soybeans, and wheat, among others [20], contributing to the development of new drugs to assist the treatment of various diseases.

Obtaining Bioactive Peptides from Agroindustrial Byproducts

Byproducts are generated in large quantities during the

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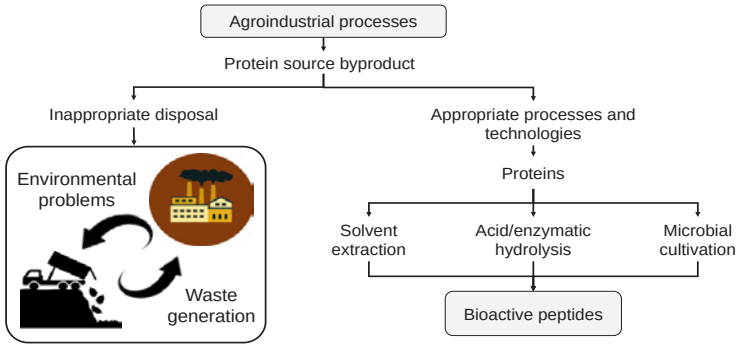

Figure 1: Methods of obtaining bioactive peptides from proteins obtained from agro industrial byproducts.

processing steps in agro-industries. In general, the byproducts have different constituents; however, as similarities, they have a high concentration of proteins that are generally underutilized [20], which is attractive for obtaining bioactive peptides [21]. The use of appropriate processes and technologies provides for full use of these byproducts, contributing to the reduction of environmental impacts, which is more necessary in the current scenario [5].

Peptides can be obtained and/or extracted from protein sources, basically through the use of solvents, controlled systems of acidic or enzymatic hydrolysis, or even by microbial culture (Figure 1) [22].

The enzymatic hydrolysis method is the most used since it does not result in the production of residues of organic solvents or toxic products in the final product [22]. Enzymatic hydrolysis has greater specificity and allows better control of the process, resulting in changes in the molecular size as well as inter- and intramolecular binding forces of molecules, improving their functional properties [23]. In addition, it is performed under pH close to neutral and low-temperature conditions with adequate production of biologically active and health-beneficial compounds [24].

Arterial Hypertension and the Role of Bioactive Antihypertensive Peptides

Arterial hypertension contributes to approximately 9.4 million deaths per year, and it is considered a primary cause for the appearance of several pathologies associated with the cardiovascular system, such as myocardial infarction and stroke [25]. Although arterial hypertension represents an independent and continuous risk factor for cardiovascular disease, it does not occur in isolation and, therefore, has been associated with the occurrence of metabolic syndrome. Recommendations for the prevention and control of hypertension include addressing the multiple risk factors presented by the individual by the occurrence of desired health behaviors (physical activity and the adoption of a healthy diet) [26].

Hypertension develops from the interaction between genetic, environmental, and other factors, such as abnormalities in the vessel, resistance due to vascular inflammation, and/or endothelial dysfunction [27]. The regulation of blood pressure involves a series of different metabolic pathways, while control can be done through the activity of blocking calcium channels, anti-atherosclerotic effect, and through the action of vasorelaxation of the endothelium. Endothelial cells secrete various vasoactive agents, such as vasodilator Nitric Oxide (NO), prostacyclin, and Endothelium-Derived Hyperpolarizing Factor (EDHF), as well as the Endothelin Vasoconstrictor 1 (ET-1), Angiotensin II (Ang II), and thromboxane [28].

Most of the drugs used in systemic arterial hypertension act by inhibiting the angiotensin-converting enzyme, which actively participates in the renin-angiotensin system. Renin is an enzyme synthesized by the kidneys and released into the bloodstream when blood pressure drops. Renin acts enzymatically on angiotensinogen, a plasma protein of hepatic origin, transforming it into angiotensin I. Subsequently, angiotensin I is converted to angiotensin II largely in the endothelium of the pulmonary vessels due to the presence of the angiotensin-converting enzyme. Angiotensin II has several effects capable of increasing blood pressure as follows: (i) acting on arteriolar and venous vasoconstriction, increasing vascular resistance and venous blood return to the heart; (ii) acting directly on the retention of salt and water by the kidneys, which increases the volume of extracellular fluid; and (iii) acting on the secretion of aldosterone, a hormone produced by the adrenals, responsible for the reabsorption of salt and water by the renal tubules. All of the mechanisms listed play a role in raising blood pressure and bioactive peptides can act by inhibiting ACE and regulating arterial hypertension (Figure 2) [29,30].

Although several pharmacological agents are widely used in the prevention and treatment of high blood pressure, side effects such as dry and unproductive cough flushing, tachycardia, and headache have been reported [31,32]. Thus, the use of bioactive peptides obtained from agroindustrial byproducts as an alternative or as a complement to conventional pharmacological treatment [33] has stimulated enormous interest because the use of this peptides can decrease dosage levels and, consequently, the costs of this therapy.

Vegetal or animal byproducts have been used for bioactive compound obtention [34], such as bioactive peptides. These bioactive peptides produced by protein hydrolysis have been shown to exert antihypertensive activity, especially in *in vitro* studies [12,35-37]. The demonstration of the *in vitro* antihypertensive potential of bioactive peptides is important because it is possible to predict the best conditions for carrying out the hydrolysis process, as demonstrated by Nogata, Nagamine [38]. These authors demonstrated that milled whole-grain, bran, shorts, and red dog acquired ACE inhibitory activity though water-soaking treatment and the production of ACE inhibitory peptides was almost completely inhibited by pepstatin A, as

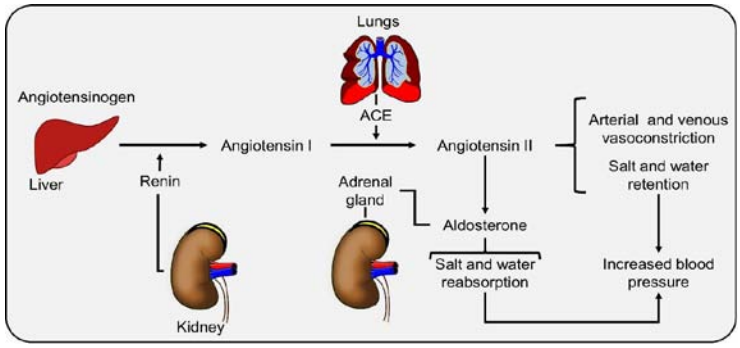

Figure 2: Generic diagram of the mechanisms involved in increasing blood pressure.

well as by the optimal pH temperature for acquiring ACE inhibitory activity of the byproduct fraction.

However, another concern is that the bioactive peptides demonstrate the same action in vitro and in vivo, which means they pass through the gastrointestinal tract without undergoing modifications and without affecting its beneficial action. In this sense, Cudennec, Violle [39] and Mäkinen, Johannson [40] showed that the antihypertensive effect in vitro of a hydrolysate obtained from a land snail (Helix aspersa) by-product hydrolysate and rapeseed meal, respectively, were maintained after gastrointestinal digestion.

Some studies have demonstrated the potential of bioactive peptides using the animal model such as: (i) Ruan, Luo [41] found a decrease of 20.7 mmHg in systolic blood pressure after 3 hours of administration of fermented soybean meal with Bacillus subtilis; (ii) Lafarga, Aluko [42] showed a decrease in systolic blood pressure between 14.3 and 36.2 mmHg in animals treated with papain hydrolysate obtained from bovine globulin and bovine serum albumin; (iii) Udenigwe, Girgih [43] observed antihypertensive effects in hypertensive rats when using gastrointestinal proteases (pepsin + pancreatin) in the hydrolysis of spent hen meat proteins, corroborating the results previously obtained by Onuh, Girgih [44], Onuh, Girgih [45], Onuh, Girgih [46], and Onuh, Girgih [47]; (iv) Mas-Capdevila, Iglesias-Carres [48] described the vasoprotective effect in rats fed with protein hydrolysates of chicken's feet, which decreased ET-1 and induced positive regulation of Sirt-1 and Nox-4 genes; and (v) Xingfei, Shunshun [49] demonstrated that rats intragastrically fed with low-dose and high-dose green tea proteolytic products after 1h demonstrated a decrease in systolic and diastolic blood pressures (SBP and DBP, respectively). Subsequently, SBP and DBP gradually increased, returning to the pre-administration level at 6h, indicating that the green tea proteolytic product possessed effective blood-pressure-lowering activity *in vivo*.

The use of bioactive peptides obtained from food industry byproducts has increased, as well as the elucidation of their antihypertensive potential. Based on this evidence, the bioactive peptide technology has been explored by the dietary supplement industry. Among the products available on the market for the general population are Vasotensin® (Metagenics), which provides peptides from beautiful fish acting formula; Ameal BP Peptide™ Tablets with Valyl-Prolyl-Proline (Vpp) and Isoleucyl-Prolyl-Proline (Ipp) hydrolyzed from casein-milk; and Blood pressure formulation combo™ (BELL Master Herbalist) with fish peptides and herbal support, among others.

Although all these supplements have claims for blood pressure reduction labeling, they can be used as a complement with other heart support programs such as prescription drugs, medical foods, and dietary supplements. It is also clear in the label as a legal disclaimer that statements have not yet been evaluated by the United States Food and Drug Administration.

Conclusion

Challenges and perspectives

The use of bioactive peptides obtained from agroindustrial protein byproducts as an alternative to pharmacological treatment has been documented and is undoubtedly an important process to enable the full use of waste generated by industries to promote added value and mitigate environmental impacts. Despite the advances, several lacunas need to be studied to enable the effective application of these components in alternative treatments, which include the need for improved and optimized development of the obtaining steps, including the extraction, hydrolysis, and purification of the peptides.

The steps must be carried out in order to obtain the structure and sequence of specific amino acids that confer antihypertensive activity. In addition, the need for stabilization of these molecules and targeted delivery to the human body must be taken into account, thus ensuring the maintenance of bioactivity and protecting against degradation during the gastrointestinal tract. In addition, process conditions must be established that allow production on an industrial scale and, still, the execution of clinical trials to prove the safety and performance of the peptides.

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