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Pay Attention to the Therapeutic Applications of Plant Peptidases: New Perspectives with Nanotechnology

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Abstract

Since ancient times the therapeutic use of plant peptidases has been recognized. The combat of a diversity of diseases involves the proteolytic activity for degradation of related peptides and proteins such as signaling molecules of inflammatory, allergic and oncologic processes, bacterium membranes, virus capsids, and collagen in fibrosis, necrotic tissues and others. Bromelain, papain, and ficin are the plant peptidases of the largest use in medicine. In the first half of 20th century, the use plant peptidases in pharmacy and medicine had increased.

The advent of synthetic drugs diminished the use of plant enzymes that gained interest again due to increased drug resistance. More recently, recombinant DNA technology contributed to the large-scale production of some plant peptidases. Nowadays, the advent of nanotechnology potentiates a variety of advances in the study and modulation of the therapeutic activity of enzymes, and this includes plant peptidases. Nanotechnology allows improving not only the use of plant peroxidases for the treatment of diseases, but also for the development of new sensors for diagnosis. Therefore, plant peptidases deserve to be considered for drug advances due to their various intrinsic properties that can be improved and modulated by the association with nanostructures.

Keywords: Plant peptidases, drugs, pharmaceuticals, inflammatory processes, nanotechnology, drug delivery, metallic nanoparticles.

Abbreviations: NPs: nanoparticles; EC: enzyme commission numbers; NCIUBMB: Nomenclature of the Committee of the International Union of Biochemistry and Molecular Biology

Opinion

The plant extracts provide a diversity of compounds useful for therapeutic uses such as oils, polyphenolic compounds and enzymes [1]. The plant proteolytic enzymes are widely used since ancient times for several applications [2]. Proteases are enzymes that promote hydrolysis of the peptidic bond of peptides and proteins. The Enzyme Nomenclature of the Committee of the International Union of Biochemistry and Molecular Biology (NCIUBMB) recommends the term peptidase for referring to these enzymes. Peptidases belong to the group 3, the hydrolases, and subgroup 4, i.e., the hydrolases of peptide bonds. The peptidases are classified according to the catalytic amino acid residue present in their active site. Thus, the peptidase types are cysteine endopeptidases (EC 3.4.22); serine endopeptidases (EC 3.4.21); aspartic endopeptidases (EC3.4.23); metalloendopeptidases (EC 3.4.24); threonine endopeptidases (EC 3.4.25) and the group with an unknown catalytic mechanism (EC 3.4.99).

Aspartic and metallopeptidases use an activated water molecule as the nucleophile agent rather than the side chain of an amino acid residue that is the catalytic agent for serine, aspartic and cysteine peptidases [3]. In living organisms, peptidases play different biological roles in food digestion, cell signaling, hormonal activation, recycling of cell components, defense against infectious and parasite agents, and others. Similarly, peptidases also have a diversity of applications and are versatile therapeutic compounds. In fact, proteolysis is useful to combat several diseases, because a lot of them involves the activity of endogenous enzymes or proteins of infectious agents.

The therapeutic action of peptidases can target signaling molecules of inflammatory, allergic and oncologic processes, bacterium membranes, virus capsids, collagen in fibrosis, necrotic tissues and others. Among several plant peptidases, bromelain, papain, and ficin deserve particular attention since they are the most plant enzymes used in therapeutics [4,5]. The enzymatic activity of bromelain includes cysteine protease and also peroxidase, acid phosphatase, and protease inhibitors [6]. Cysteine protease activity is also the mechanism of papain and ficain [3]. The therapeutic properties of pineapple, papaya, and fig extracts can derive from the proteolytic activity for cleavage of proteins and peptides involved in a disease or the inhibition of a proteolytic activity responsible for a dysfunction [4]. Figure 1A & B shows, respectively, the structure of papain and bromelain inhibitor VI extracted from pineapple stem, a cysteine protease inhibitor.

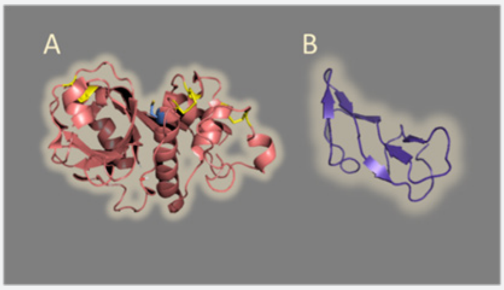

Figure 1: Products of papaya and pineapple with therapeutic properties. A) The structure of papain, with a cysteine residue of active site highlighted in blue and disulfide bonds highlighted in yellow. B) The structure of the inhibitor of cysteine proteases extracted from pineapple stem, the bromelain inhibitor VI. The data were obtained from PDB, with codes 1PPN for papain and 2BI6 for bromelain inhibitor and the artwork done using a free version of PyMOL for educational use only.

In fact, several pathological processes are related to the over expression of cathepsins and decrease of the production of their inhibitors. A typical example is the cell invasion and metastasis of gastric, breast, glioma and prostate aggressive tumors that are related to an increased expression, secretion and decreased inhibition of lysosomal proteases [7]. Numerous therapeutic actions have been described for the extracts of pineapple, papaya, and figs such as mucolytic effect, digestion improvement, acceleration of wound therapeutic, antithrombotic effect and circulatory benefits, the combat of inflammatory processes, tumor growth and metastases, and others. These remedial actions are frequently related to the proteolytic activity of these extracts and the presence of cathepsin inhibitors and a digestion aid [8,9].

These beneficial effects of pineapple, papaya, fig and other plants led people to use them in medicine since the ancient times. The development of chemistry, biochemistry and the methods for the purification of active principles allowed the identification and more efficient use of plant components. Plant peptidases were primarily used in pharmacy and medicine, in the first half of 20th century [2]. The development of synthetic drugs firstly sounded to be a more efficient and, in some cases, a cheaper alternative for the use of plant enzymes but this early enthusiasm decreased due to increasing cases of drug resistance. However, the resumption of interest in the medicinal use of plant enzymes was challenged by the need for the large-scale production of the drugs containing these active ingredients.

As enzymes are proteins, their mass production for medicinal use has been made possible by the advent of recombinant DNA technology. However, the challenge for therapeutic use of plant peptidases is not restricted to industrial scale production. For the development of therapeutic agents, it is important to consider some interconnected factors such as efficient delivery, target specificity, and toxicity. The toxicity of plant peptidases has been described as weak and limited to the exposure to dust or aerosol of their solutions [10]. However, with the exploration of other plant extracts different types of toxicity can rise. Therefore, in the same way, as molecular biology contributed to circumvent the problem of scalable production of plant peptidases for therapeutic and industrial uses, the nanotechnology may help to improve specificity, delivery, and decreasing toxicity.

Plant extracts and peptidases purified from these sources can act both as reducing and stabilizing agents for the synthesis of metallic nanoparticles [11] and even contribute to the enhancement of the enzymatic activity [12]. Proteolytic enzymes associated to nanostructures have the potential for therapy and sensing for diagnosis [13-17]. As an example, von Maltzahn et al. [18] described a model for detecting two enzymes MMP2 and MMP7 (matrix metallopeptidases-2 and -7, respectively) associated with cancer metastasis. Two populations of super paramagnetic nanoparticles are coated with avidin or biotin. These particles are maintained dispersed by the presence of polyethylene glycol linked to substrates of the enzyme MMP2 and MMP7. The authors designed two configurations for sensing. The NP population containing biotin has a substrate of MMP2, and that containing avidin has the substrate for MMP7. In this configuration, the aggregation of NPs by the removal of PEG-peptide coating occurs if both enzymes are present. In the other setting, only the NPs containing avidin has the coating of peptide-PEG, but the peptide linked to the polymer has the sequences that are a substrate of both MMP2 and MMP7. Therefore, the NP aggregation will occur if MMP2 or MMP7 is present. Also, the increase in enzymatic activity may be achieved by the association of the enzymes with nanoparticles [13], [19-21].

Conclusion

In conclusion, we have the opinion that the conciliation of the therapeutic use of plant peptidases, a practice that persists from ancient times, with the most recent advances of nanoscience and nanotechnology open new perspectives for pharmacology and diagnosis. We can take advantage of this strategy for a green synthesis and stabilization of metallic nanoparticles, for the improvement of a desirable therapeutic enzymatic activity, for the improvement of delivery, specificity and toxicity lowering. In some cases, the nano particulate system might act as diagnosis and treatment, i.e., the theranostic properties.

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Conflict of Interest

Authors declare that no economic interest or conflict of interest exists

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