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Structural and Functional Characteristics of Hydrolytic Enzymes of Phytophagon Insects and Plant Protein Inhibitors (Review)

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Abstract—The data on proteolytic, cellulolytic, proteolytic, and amylolytic enzymes of insect pests and their inhibitors from plants are considered and generalized. The structure, physical, chemical and functional properties of enzymes and inhibitors are described. The analyzed data showed that the search for possible ways to improve the inhibitor activity of insect hydrolases is relevant for the creation of pesticide alternatives.

Keywords: hydrolytic enzymes, hydrolases inhibitors, phytophagon insects, plant defense

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INTRODUCTION

Improvement of the resistance of agricultural plants to diseases and pests is one of the most important problems in environmentally friendly crop production. An understanding of the mechanisms of the interrelationships between plants and phytophagous organisms can aid in solving the problem. The hydrolytic enzymes of insect pests and pathogenic microorganisms are an important link in their interaction with plants, since they provide an efficient breakdown of plant polymers, which form the basis of the feed substrate [1–4]. The activity of various types of hydrolases, cathepsin-like and trypsin-like proteases [1–4], endoglucosidases [5, 6], cellobiohydrolases and β glucosidases [7, 8], and α amylases [9, 10], was revealed in the tissues of phytophagous organisms.

Suppression of the activity of hydrolytic insect–pest enzymes is an effective way to implement plant defense mechanisms [11, 12]. It is known that specific inhibitors capable of neutralizing the action of the digestive enzymes of insects are found in the tissues of various plant species [13–19]. Thus, the presence of inhibitors of cysteine and serine proteases in plants [13–15], cellulases of various nature [16], pectinases [17] and amylases [18, 19] has been described. In response to plant contact and consumption by insects, there is an intense accumulation of hydrolase inhibitors in both the affected and intact organs [11, 20–22].

Studies on phytophagon hydrolases and specific inhibitors from plant tissues are of interest, both from the point of view of the molecular mechanisms of interaction between plants and phytophagous organisms and the search for effective and environmentally friendly methods to protect crops from insect pests.

Proteolytic enzymes. Of the hydrolytic enzymes of phytophagous insects, the greatest amount of experimental data has been obtained on the structure and physiological properties of proteases (Table 1).

Cysteine proteases. These proteases play an important role in the digestion of plant food in a wide range of coleoptera [23, 24]. Thus, the proteolytic enzymes of the Colorado potato beetle are represented mainly by cysteine proteinases, which are similar in properties to the B and H cathepsins of mammals [14, 25, 26].

Most cathepsin-like enzymes contain a cysteine residue, which plays the role of a nucleophilic group, in the active center and a histidine residue, which is part of the catalytic center of proteases [27]. These enzymes are characterized by a broad specificity; however, some of them cleave the substrate, mainly with certain amino acid residues. Most of the cathepsin-like enzymes are endopeptidases, and a small percentage of them are carboxy- and aminopeptidases. It was shown that their activity is inhibited by both synthetic and natural inhibitors. These enzymes are usually localized in the cavity of the insect midgut, and the pH-optimum for the enzymatic activity in most of them ranges within pH values of 5–7 [28].

Serine proteases. The chymotrypsin-like protease of Coleoptera has optimal activity at a pH of 5.5–6.5 and is sensitive to inhibitors of serine proteases [29]. The predominant component causing chymotrypsin-like activity is a protein with a molecular mass of about 63 kDa. There is also a minor component with a

Table 1. Information on some insect pest hydrolases and their plant inhibitors

Hydrolases and inhibitors	Representatives	Insect and plant species	Molecular mass, Da	Reference
Cysteine proteases	Cathepsin-like cysteine proteases	*Leptinotarsa decemlineata*	38000	[14, 25–28]
Serine proteases	Chymotrypsin-like proteinase	*Coleoptera, Lepidoptera*	63000; 100000	[29]
	Carboxypeptidase B	*Helicoverpa zea*	35000	[30]
Aspartate proteases	Cathepsin D-like proteinase	*Spodoptera exigua, Dysdercus peruvianus, Oulema melanopus*	42000	[32, 33]
Cellulases	GHF-5	*Mesosa myops*	36000	[49]
		Nephotettix cincticeps	40000	[50]
		Apriona germari	47000	[47]
	GHF-9	*Tribolium castaneum*	49500	[64]
	GHF-45	*Batocera horsfieldi*	25000	[46]
Pectinases	Polygalacturonase	*Sitophilus oryzae*	39000	[74]
Amylases	Alpha amylase	*Tenebrio molitor*	50000	[81]
Inhibitors of serine proteases	Kunitz-type	Different species	20000	[88, 92]
	Bowman–Birk	Different species	8000–10000	[93–96]
	pot II	*Solanum tuberosum*	5500	[97]
	MTI2	*Sinapis alba*	7000	[98]
	MCTI	*Momordica charantia*	3000	[99, 100]
	RATI	*Eleusine coracana*	14000	[101]
Inhibitors of cysteine proteases	Cystatin-1	Different species	13000	[102–104]
Inhibitors of metalcarboxypeptidases		*Solanum tuberosum, Solanum lycopersicum*	4000	[106, 107]
Inhibitors of cellulases	Phenolic compounds	Different species	More than 10000	[108–112]
Inhibitors of pectinases	PGIP	Different species	40000	[113–122]
Lectin-like inhibitors of amylases	αAI-1, αAI-2	*Vicia faba*	23000	[132]
Knottin-like inhibitors of amylases		*Amaranthus hypocondriacus*	3500	[130]
Kunitz-type inhibitors of amylases		*Hordeum vulgare, Triticum aestivum, Oryza sativa, Vigna unguiculata*	22000	[132, 133]
Purothionine-like inhibitors	SIα 1, SIα 2, SIα 3	*Sorghum bicolor*	5000	[134]
CM proteins		*Gramineae*	13000–18000	[135]
Thaumatin-like inhibitors	Zeamantine	*Zea mays*	22000	[136–138]

molecular mass of about 100 kDa. The pH optimum for the enzymatic activity of serine proteases varies greatly among different insect species. In particular, Lepidoptera serine proteases with optimal activity at an alkaline pH (~10) are known [30]. In the digestive system of the Colorado potato beetle larvae, exopeptidases, which are proteases similar to carboxypeptidase A and leucine aminopeptidase, were also found. Unlike most digestive proteases, aminopeptidases are localized in epithelial tissue.

Aspartate proteases. Aspartate insect proteases are relatively less well studied. Most of them are charac-

terized by optimal proteolytic activity in the acidic pH range (about 3–5) [31]. Cathepsin D-like aspartate proteinase exhibits maximal enzymatic activity at pH 4.5 [32, 33]. This proteinase is known to play an important role in the initial digestion of plant food proteins, in particular, ribulose bis phosphate carboxylase oxygenase, the major protein of potato leaves [34]. The subsequent cleavage of food proteins is carried out by cysteine (cathepsin B- and H-like) and serine (chymotrypsin-like) proteinases.

The release of proteolytic enzymes into the intestinal cavity of an insect depends not so much on the amount of food but on the composition of the proteins in it. Both the direct effect of food proteins on the epithelial cells of the midgut and hormonal effects associated with food ingestion in the body are involved in protease secretion [35]. Enzymes form in the intestinal cells in a membrane-bound form and accumulate in the vesicles, which, in turn, are associated with the cytoskeletal structure, and are also secreted by epithelial cells as special complexes [36], after which the proteases move into the intestinal lumen.

Cellulolytic enzymes. Cellulases in insect tissues are represented by a cellulase complex consisting of three types of hydrolases (Table 1): endoglucanases, which hydrolyze β-1, 4 bonds in the cellulose chain at a random location inside the molecule; cellobiohydrolases or C_1-cellulases, which cleave cellobiose from the end of the cellulose chains; and β glucosidases and cellobiases, which cleave glucose from the nonreducing end of the cellulose chain [38]. Insects have their own cellulase and microbial cellulase of symbiotic microorganisms (different genera have C_x- or C_1-, or both enzymes at the same time) [39–41].

The cellulase complex of bacteria includes endoglucanase, cellobiase, and cellobiohydrolase [42]. It is known that bacteria are able to synthesize both cellular and extracellular enzyme forms. Cellulose-destroying microorganisms use two different mechanisms of cellulose cleavage [43, 44]. Most aerobic microorganisms secrete cellulase molecules, which may contain a carbohydrate-binding domain at the N- or C-terminus of the polypeptide chain. Anaerobic microorganisms, as a rule, form large (more than 1000 kDa) multienzyme complexes, cellulosomes, which are usually attached to the outer cell surface. Most of the cellulases in the cellulose have no carbohydrate binding domain; however, it is present in the scaffoldin protein, which is bound to the cellulases. Analysis of the genomic sequences of aerobic and anaerobic cellulolytic bacteria showed that there is also a third mechanism characterized by the absence of both cellulose and carbohydrate-binding domains in the enzyme molecule [45]. The cellulases, both those in the cellulose and freely secreted cellulases, have a high similarity in the catalytic domain structure and catalysis mechanisms.

At least six representatives of endoglucanases were isolated from various insect species. They include enzymes *Psacothea hilaris* [https://www.ncbi.nlm.nih.gov/protein/928430643] and *Batocera horsfieldi* (25 kDa) [46], *Apriona germari* (25 and 47 kDa) [47, 48], *Mesosa myops* (36 kDa) [49], *Nephotettix cincticeps* (40 kDa) [50], and *Nasutitermes takasagoensis* (47 kDa) [51, 52]. Two isoforms with molecular masses of 41 and 42 kDa were isolated from *Reticulitermes speratus* [53, 54].

Based on a comparative analysis of amino acid sequences, more than 160 glycosyl-hydrolase families, which are combined into 18 clans [http://www.cazy.org/Glycoside-Hydrolases.html], have been isolated.

Endoglucanases of a number of insects belong to the family of glycosyl hydrolases, which is designated as GHF-5, [49, 50, 55]. The representatives of this family have a common structural motif $(\beta/\alpha)_8$-barrel [56, 57]. Most cellulases of this family are also characterized by the presence of conservative amino acid residues Arg79, His122, Asn169, and Glu170, which serve as proton donors for the cleavable β-1,4-glycosidic bond. The catalytic center is formed by His254, Tyr256, and Glu307, which are nucleophilic residues transmitting hydroxyl residues to the cleavable glycosidic bond [58, 59]. Arg79, His122, Asn169, Glu170, and Glu307 take part in the formation of the catalytic center. Such a structure is typical for the endoglucanases of all of the studied insects. It should be noted that a similar structure was also described for bacterial cellulases, which made it possible to put forward a hypothesis on the horizontal gene transfer of the enzymes [60].

Endoglucanases belonging to the structural family designated as GHF-45 [61, 62] were isolated from a number of beetles. Studies of the three-dimensional structure of proteins of this family showed the presence of six β barrels and three α helices in their molecule. Asp121 acts as a donor of protons for the catalytic center and Asp10 acts as a donor of the nucleophilic group, although they are conservative residues.

Glycosyl hydrolases of the GHF-9 structural family were isolated from some insects. The three-dimensional structure of their catalytic domain was shown to be similar to the structure of a number of endo- and exocellulases of fungi [63–65]. Glycosyl hydrolases of this type cleave the residues of 5-membered cellulose sugars to tetrose or triose with the reversal of the anomeric carbon configuration, while 18 amino acid residues participate in the binding of the catalytic center to the substrate.

Many endoglucanases of phytophagon insects are known as single domain proteins, i.e., they contain only the catalytic domain, whereas many parasitic fungi cellulases contain both catalytic and cellulose-binding domains, as well as proline, threonine, and serine rich residues connecting two domains [66, 67]. In addition to the catalytic and cellulose-binding domains, other elements may be present in the cellulase structure, including an additional catalytic

domain, fibronectin III-like domains, as well as repeated hydrophobic sequences of cohesion-dokerin type.

Pectolytic enzymes. Pectinases are a complex of enzymes that can be divided into at least seven groups according to the nature of the enzymatic activity (Table 1) [68]. The division of pectinases into two large classes is generally accepted. Pectin methyl esterases and pectine depolymerases are, in turn, are divided into polygalacturonases and pectate lyases. Protopectinases, which cleave protopectin, and pectin transaminases, which are capable of cleaving the pectin uranoid bonds without prior demetoxylation, were isolated [69, 70].

A number of studies showed that the presence of polygalacturonase in insects was acquired, as believed, as a result of horizontal gene transfer [71–73]. Comparative analysis of genetic sequences suggests that bacteria were the most likely source of the transferred genes [72, 74].

A spatial structure was established for rice weevil pectinase. It is based on a right-handed helix formed by β strands. Comparative analysis of this structure indicated that rice weevil pectinase originated from bacterial lipoprotein [74].

Amylolytic enzymes. The amylase content and activity in insect tissues substantially depends on the nature of the food substrate and the stage of insect development [9, 75]. One of the reasons for this dependence may be the effect of food on the insect's internal environment, in particular, on the pH level. The coleoptera amylases exhibit the greatest activity in an acidic environment, the amylases of dipterans do so in a neutral environment, and the amylases of lepidopterans are most active in an alkaline environment [10, 76]. Since amylase expression is determined by multiple gene copies [10], it appears that this makes it possible to regulate the specificity of their action and physicochemical properties to overcome the protective properties of plants.

The α amylase of the Colorado potato beetle functions in a wide range of pH values (from 6.0 to 10.0) and temperatures (from 25 to 45°C) with an optimum around a pH of 6.5 and 37°C [9]. The maximum amylolytic activity is noted in the anterior intestine of the Colorado potato beetle, whereas it is rather small in the middle intestine and absent in the posterior part. Thus, α amylase of a cabbage butterfly has a molecular mass of 80 kDa, the optimal pH is about 8.0, and the optimum temperature is 35°C [77]. The optimal pH and temperature are 7.0 and 40° C for amylases of bean aphid [78]; 5.2 and 35°C for the larvae of barbel beetles [81]; 4.0 and 50°C for amylases of the intestine and 6.0 and 60°C for those of the head glands in the cryptolemus and mealybug predator [80]. The spatial structure of α amylase of the meal worm is known. This protein with a molecular mass of about 50 kDa consists of two domains, one of which belongs to the α/β-hydrolase family, and the other belongs to β hydrolases [81].

The considerable variety of physicochemical properties of insect amylases appears to cause differences in the specificity of their action and the mechanisms of regulation.

Protease inhibitors. The presence of proteolytic enzymes is important for plant food absorption by pests; therefore, they are attacked by plant defense systems [11, 82–85]. It is known that there is a sharp increase in the content of trypsin and chymotrypsin inhibitors in plants when the leaves of tomato and potato are damaged by the Colorado potato beetle. During long-term damage, inhibitors of cysteine and aspartate proteinases are also synthesized [14]. A number of insects synthesize proteases that are insensitive to plant inhibitors [86], which leads to significant plant damage.

The increase in the content of protease inhibitors in plants occurs, as a rule, not due to an increase in the concentration of constitutive compounds but due to the synthesis of their new, special forms [87]. These forms, which form in response to stress, have a significantly higher specificity with respect to insect pest proteases than the inhibitors that are constantly present in plant tissues.

There are a significant number of known protease inhibitors from different plant species. They constitute about 10–15 families that differ in the amino acid sequence and specificity with respect to a given protease class [88]. Thus, inhibitors of serine, cysteine, aspartate, and metalloproteases are distinguished [34].

Serine protease inhibitors. These inhibitors have been found and described for many plant species and, apparently, are a universal component of plant tissues [89]. At the same time, enzymes of this type predominate in plants. Serine protease inhibitors are competitive inhibitors and act on a practically identical mechanism [90]. The structure of molecules in many their representatives is similar. Thus, as a rule, the active center is located on a disordered loop stabilized by disulfide bonds [34, 91].

The plant inhibitors (called Kunitz-type inhibitors) are described in the most detail. They are ~20-kDa proteins containing one or two disulfide bonds and one enzyme binding site [88]. These inhibitors have a beta-globule structure containing 10–12 antiparallel beta strands connected by long loops. An active center that can form hydrogen bonds with the binding center of the enzyme is on one of the loops. Two conservative cysteine residues that form a disulfide bond and thus support the active center and inhibitory activity of the protein was shown to be present in the inhibitor molecule [92].

Bowman–Birk inhibitors. Bowman–Birk inhibitors are a common family of plant inhibitors of proteinases (serine proteases). They are proteins with a molecular mass of about 8–10 kDa that are rich in cys-

teine residues and have two enzyme-binding sites. The inhibitor's polypeptide chain consists of 71 amino acid residues and is stabilized by seven disulfide bonds [93]. Their molecules contain a portion of the clearly detectable region of the "nucleus," outside of which are located cysteine residues and the serine residues forming the binding site. The N- and C-terminal regions of the protein are highly variable, and the central region is conservative and almost unchanged in all protease inhibitors of the Bowman–Birk type [94–96].

Type II potato proteinase inhibitors (pot II). The most important role in the plant protection system of the family of solanaceous pests is played by a family called potato type II proteinase inhibitors (pot II). Inhibitors of this family always accumulate in response to plant infection with a pathogen or injury. The proteins of the pot II family are characterized by such phenomena as tandem duplication, domain exchange, and rearrangement of H-(heavy) and L-(light) fragments. Famous members of the family contain two to nine repeating sequences consisting of about 50 amino acid residues, including the reaction center [97].

Two different trypsin inhibitors, MTI and MTI2, were found in runchweed seeds. MTI has characteristics similar to a Kunitz-type trypsin inhibitor. MTI2 is a highly active and thermostable inhibitor; it is a polypeptide consisting of 63 amino acid residues, is rich in cysteine and glycine residues, and does not have structural homology with other known plant serine protease inhibitor families [98].

Family of Momordica Charantia Trypsin Inhibitor (MCTI) inhibitors. Inhibitors of this family contain about 30 amino acid residues. Their amino acid sequence and spatial structure were established [99, 100].

There is a known bifunctional inhibitor of α amylase and trypsin from the seeds of African millet (RATI). It consists of 122 amino acid residues and contains five disulfide bonds. Its amino acid sequence and spatial structure have been established [101].

Inhibitors of cysteine proteases. Cysteine protease inhibitors have been well studied in individual plants. NMR studies of the structure of one of the representatives of this group of inhibitors, cystatin-1, showed the presence of a well-defined main globule, α helix, and five antiparallel β sheets in the molecule [102]. Similar structures were found among animal proteins with similar functional activity. Several enzymes with similar structures and action mechanisms but different inhibition constants were shown to be present in the same plant in a number of studies [103, 104]. Plant cystatins are characterized by the presence of two disulfide bonds located in the C-terminal region of the molecule. Cystatins are composed of ~115 amino acid residues and have a molecular mass of ~13 kDa.

Inhibitors of aspartate proteases. These inhibitors are structurally similar to Kunitz-type trypsin inhibitors from soybean [34]. Most aspartate proteases from the tissues of various animal species have a similar molecular structure, which corresponds to the specific structure of their plant-derived inhibitors. The center of the inhibitor binding is located in the molecule region containing a loop between two β strands [105].

Metalcarboxypeptidases inhibitors. These inhibitors from potato and tomato are peptides with a molecular mass of ~4 kDa. They function according to a competitive mechanism and effectively inhibit carboxypeptidases in both animals and microorganisms. However, serine carboxypeptidases of fungi and plants are not affected by them [106, 107].

Cellulase inhibitors. Inhibitors of cellulolytic enzymes have been found in the organs of plants of various families (in leaves, flowers, fruits, seeds and stems) [16, 108]. Natural cellulase inhibitors are characterized by a fairly large molecular mass (more than 10 kDa), thermal stability, stability during dialysis, and the action of solutions of weak acids, alkalis, and precipitating substances (e.g., TCA) [109].

Cellulase inhibitors are phenol polymerization products. They are often found in plants in combination with amylase and pectinase inhibitors. Different varieties of the same plant species contain an unequal amount of cellulase inhibitors, and cellulases of different origin differ in their susceptibility to inhibitors [110, 111]. The highest tannin activity among tree species is found in *Salix pentandra*, along with *Betula pendula, Betula nana, Betula pubescens, Salix caprea*, and *Pinus sylvestris* [112]. The ability to suppress the activity of exogenous cellulases is also shown for coumaric, ferulic, and sinapic acids [108], as well as for some substances of a carbohydrate nature. Thus, cellulase inhibitors, which are oligosaccharides consisting of a mixture of xylo- and glucooligosaccharides, were isolated from *Triticum aestivum* [108].

The interaction of plant inhibitors with insect cellulases (unlike microorganisms) has not been studied enough, although it can be assumed that the data obtained for microorganisms may also be applicable to insects. Thus, the natural glycosylated flavonoids are potential inhibitors of insect cellulases (as well as bacterial ones) [16]. Protein fractions of *Azdirachta indica* and *Buxus sempervirens* leaf extracts suppressed the activity of the powdery beetle endoglucanases [112].

Pectinase inhibitors. There are compounds in plant tissues with the ability to slow the enzymatic hydrolysis of pectins. They are found in both vegetative and generative plant organs: leaves, fruits, tubers, stems, etc. (Table 1) [113]. Natural pectinase inhibitors are soluble in water and organic solvents and are thermostable. They completely or partially inactivate the enzymes that cleave pectins. Proteins that inhibit polygalacturonases of pathogenic microorganisms and insect pests (PGIPs) are found in both mono- and dicotyledonous plants [114–117]. An increase in the expression of PGIP-encoding genes in response to insect injury was shown [118, 119]. PGIPs belong to a large class of plant proteins that participate in inter-

molecular interactions and include leucine-rich repeats (LRRs) [120]. The presence of these repeats is necessary for the formation of a labile structural carcass that provides interprotein interaction. The elasticity of the structure allows for some modification of the shape of the receptor site if needed, just as antibodies can slightly change the configuration when they bind to the antigen [114].

Studies with transgenic plants on gene blocking or overexpression confirm that proteins with LRR play a significant role in the processes of growth and development of plant tissues, as well as in their interaction during attacks on phytophagon organisms, since many products of R genes belong to this group [121]. However, the mechanism of the functioning of these proteins is not well understood. Proteins with LRR have different localizations. Some of them are found in the cytosol, while others are in the plasma membrane and have intracellular and extracellular domains. The protein inhibitor of polygalacturonase is a fully extracellular protein (eLRR). The presence of PGIP in the apoplast is confirmed by the fact that it is extracted from tissues by vacuum infiltration [114]. The vast majority of known PGIPs are glycoproteins with a molecular mass of about 40 kDa. At the same time, the share of carbohydrates in their molecules accounts for 20% of the total mass [122]. In PGIP molecules from different plants, the number and position of glycosylation sites vary, which can probably contribute to the determination of the specificity of interaction with ligands. The degree of glycosylation of the same protein may depend on its expression site [114]. The pPGIP genes were cloned from different plant species and combined on the basis of significant similarity into small families [121].

Amylase inhibitors. Amylase inhibitors, as well as proteinase inhibitors, are found in plants of various families: cereals (*Gramineae*), legumes (*Fabaceae*), solanaceous (*Solanaceae*), and others (Table 1) [123, 124]. Protein inhibitors selectively interact with amylases and form inactive "amylase-inhibitor" complexes [125]. Bifunctional inhibitors (BFIs), which are able to interact not only with α amylase, but simultaneously with proteases, are also known. The most studied BFI are α amylase and subtilisin inhibitors from barley and wheat [124]. BFIs are also known to act on proteinase K and α amylase from wheat [127], α amylase and chymotrypsin from maize [128], α amylase from mammals, and trypsin [126]. It was shown with crystallography and computer simulation that hydrogen bonds, ionic, and, to a lesser extent, hydrophobic interactions are involved in the formation of the amylase-inhibitor complex of amylase [129]. α-Amylase inhibitors are used by plants as a protective mechanism against insect pests, as well as pathogenic microorganisms [129, 130]. Based on their structural similarity, six different families of protein inhibitors of plant α amylase (alpha-amylase inhibitors, AAI) are distinguished: lectin-like, knottin-like, γ purothionine–like, thaumatin-like, and Kunitz-type α-amylase inhibitors and CM (chloroform-methanol) proteins [131].

Lectin-like inhibitors. Two lectin-like α-amylase inhibitors, designated αAI-1 and αAI-2, are identified in the buds of beans. These proteins exhibit different specificities for α amylases due to mutations in their primary structure. Thus, αAI-1 inhibits the α amylases of mammals and some insects but does not inhibit the α-amylase activity of the Mexican weevil. The αAI-2 inhibitor is active against α amylases of *Zabrotes subfasciatus* but does not inhibit α amylases of the aforementioned animal groups [132].

Knottin-like inhibitors. The major α amylase inhibitors present in the seeds of *Amaranthus hypocondriacus* L. are polypeptides, consisting of 32 amino acid residues with three disulfide bridges. AAI inhibits α amylases of *T. castaneum* and *Prostephanus truncates* but does not inhibit mammalian α amylases [130].

Kunitz-type inhibitors of α amylases. This group of inhibitors is found in such cereal crops as barley, wheat, and rice [132], as well as in legumes, in particular, in cornice [133]. α-Amylase inhibitors from *Vigna unguiculata* L. inhibit the activity of α amylases in mammals and insects to different degrees [133]. α-Amylase/Subtilisin inhibitors (BASI) have bifunctional properties; they are involved in plant protection and act as endogenous regulators of α amylase activity [132].

γ-Purothionine-like inhibitors. Representatives of this family consist of 47–48 amino acid residues and have a pronounced inhibitory activity against insect α amylases. SIα 1, SIα 2, and SIα 3 proteins isolated from *Sorghum bicolor* suppress the α-amylase activity of the cockroach and locust but do not affect α amylases of human saliva. This group of inhibitors does not inhibit pancreatic α amylases in pigs, barley, or *Bacillus sp*. All three isoforms contain eight cysteine residues, which form four disulfide bridges. [134].

CM proteins. Chloroform and methanol soluble proteins (CM proteins) belong to a large family of cereal (*Gramineae*) seed proteins. It consists of 120–160 amino acid residues and has five disulfide bonds. CM proteins possess a typical α-amylase/trypsin domain [135]. This structural feature determines their ability to inhibit the activity of both α amylases and trypsin-like enzymes [135].

Thaumatin-like inhibitors. This family contains proteins with a molecular mass of about 22 kDa that are homologous to the thaumatin protein from fruits of *Thaumatococcus daniellii* and suppress enzymes of fungi, bacteria, and insects [136]. Zeamantin, isolated from corn, is a typical representative of this family of inhibitors. It exhibits inhibitory activity against insect α amylases but is not active against mammalian α amylase. The protein structure consists of 13 β layers, 11 of which form a β sandwich [137, 138]. Zeamantin is used as an antifungal drug, because it has the ability to bind the β-1,3-glucan of the fungal cell wall [131].

CONCLUSIONS

Thus, the available information on the hydrolytic enzymes of insects and their inhibitors from plants suggests that suppression of the activity of exogenous hydrolases by specific inhibitors is an effective way to use the protective properties of the plant organism against phytophagon organisms. It can be assumed that the use of hydrolase inhibitors as biopesticides will be a promising and environmentally safe way to protect plants from insect pests and pathogenic microorganisms. Compared with traditional "chemical" pesticides, they act more specifically and have a less negative impact on the environment. At the same time, issues on the chemical resistance of biopesticides, as well as the biological and economic efficiency of their use, remain unresolved [139]. The creation of drugs with a protective action based on the induction of the synthesis of hydrolase inhibitors in plant tissues may solve these issues.

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