Applications of Peptides in Health Management and Agriculture

Subjects: Biotechnology & Applied Microbiology

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Numerous bioactive peptides have been identified from edible insect species, including peptides that were enzymatically liberated from insect proteins and endogenous peptides that occur naturally in insects. The peptides exhibited diverse bioactivities, encompassing antioxidant, anti-angiotensin-converting enzyme, anti-dipeptidyl peptidase-IV, anti-glucosidase, anti-lipase, anti-lipoxygenase, anti-cyclooxygenase, anti-obesity, and hepatoprotective activities. Such findings point to their potential contribution to solving human health problems related to inflammation, free radical damage, diabetes, hypertension, and liver damage, among others. Bioactive peptides may have a positive impact on body functions and thus benefit human health. New information reporting their beneficial effects on the health of livestock and plants is also emerging. Bioactive peptides may be produced endogenously in humans, animals, and plants.

antioxidant antimicrobial bioactivity entomophagy livestock nutraceutical peptide purification protein hydrolysate protein hydrolysate

1. Introduction

Bioactive peptides may have a positive impact on body functions and thus benefit human health [1][2]. New information reporting their beneficial effects on the health of livestock and plants is also emerging. Bioactive peptides may be produced endogenously in humans, animals, and plants. Furthermore, such peptides can also be released from protein sources by enzymatic hydrolysis or prepared by chemical synthesis [3][4]. While bioactive peptides identified from hydrolyzed food proteins often range between two and twenty amino acid residues, longer endogenous peptides that occur naturally in humans and animals have been discovered [5]. The composition and sequence of amino acids determine the activity of bioactive peptides [6]. Bioactive peptides play important roles in the cardiovascular, immune, nervous, digestive, and endocrine systems. They represent a new generation of bioactive regulators, displaying hormone or drug-like activities, and exhibiting antioxidant, anticancer, antithrombotic, antihypertensive, anti-obesity, anti-inflammatory, opioid, mineral binding, immunomodulatory, antiaging, and antimicrobial effects [7][8][9][10][11]. Bioactive peptides exhibit high specificity in terms of target tissues and consequently possess low or no toxicity. Importantly, they are effective at even relatively low concentrations, which is especially important in the treatment of chronic diseases [5].

2. Purification and Identification of Bioactive Peptides from Insect Protein Hydrolysates

In the past 10 years, enzymatic hydrolysis has been frequently adopted as a means of producing bioactive peptides from the proteins of edible insects. In such studies, silkworm pupae were relatively popular for the purpose of bioactive peptide discovery [12][13][14][15][16]. **Figure 1** shows a general workflow employed by many studies in the discovery of bioactive peptides.

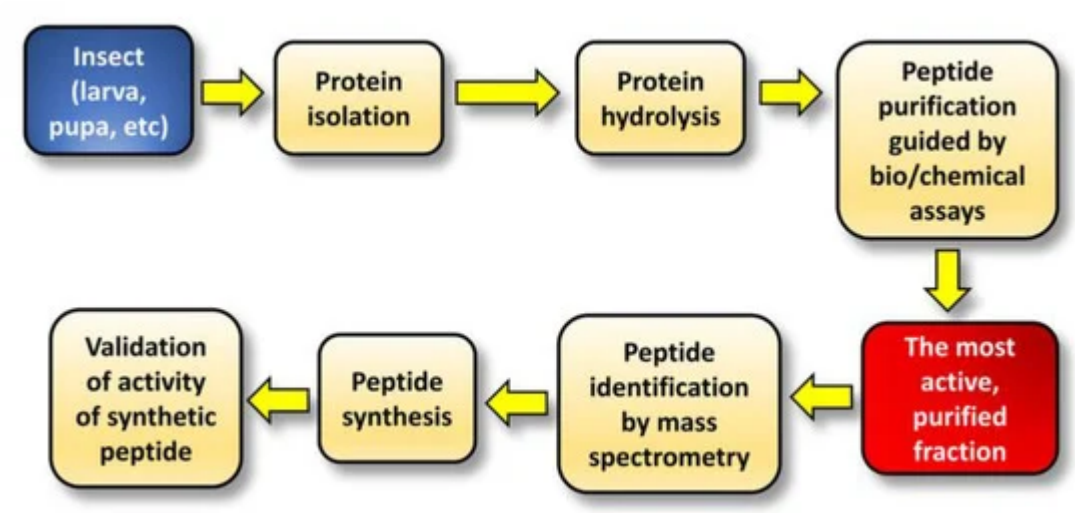

Figure 1. General workflow commonly adopted by researchers in the discovery of bioactive peptides from insect protein hydrolysates.

Among the numerous commercially available proteases, alcalase, flavourzyme, and Promod 278P were found to effectively generate functional hydrolysate/peptides from edible insects, leading to the discovery of antioxidant, anti-angiotensin-converting enzyme (ACE), anti-dipeptidyl peptidase-IV (DPP-IV), anti-obesity and hepatoprotective peptides (**Table 1**). However, alcalase received the most attention as it produced more potent peptides [12][13][17]. This could be because alcalase exhibits both endo- and exo-protease activities, which allows a broad specificity in hydrolysis sites [12], thus providing relatively extensive hydrolysis of the insect proteins. Furthermore, some studies used multiple proteases to generate insect protein hydrolysates, either through sequential hydrolysis with different proteases or in vitro simulation of gastrointestinal digestion in which a combination of multiple gastrointestinal proteases was used. Such use of multiple proteases could improve the degree of hydrolysis and yield more low-molecular-weight peptides when compared to only using a single enzyme in the hydrolysis of insect proteins [14][15][16][18].

Table 1. Examples of purification and identification methodologies used in the discovery of bioactive peptides from insect hydrolysates.

Insect	Peptide Sequence (Validated Activity)	Enzymatic Hydrolysis	Peptide Purification Strategy	Peptide Identification	Reference
Larva of the Japanese rhinoceros beetle (*Allomyrina dichotoma*)	EIAQDFKTDL (Anti-obesity) AGLQFPVGR (Hepatoprotective)	Promod 278P *, pepsin, trypsin, protease NP, pancreatin, alphalase NP, alkaline protease, alcalase, neutrase, protamex	• UF • IEC • RP-HPLC	• MS/MS analysis	[19][20]
Larva of the white-spotted flower chafer (*Protaetia brevitarsis*)	SY, PF, YPY, WI (Anti-ACE)	Flavourzyme	• UF • GFC	• LC-MS/MS	[21]
Mealworm (*Tenebrio molitor*)	LPDQWDWR, APPDGGFWEWGD (Anti-DPP-IV)	Flavourzyme *, alcalase, papain, trypsin	• GFC	• LC-MS/MS	[22]
Mealworm (*Tenebrio molitor*)	LE, AKKHKE (Hepatoprotective)	Alcalase *, flavourzyme, neutrase	• UF • Solid-phase extraction • RP-HPLC	• LC-MS • LC-MS/MS	[17]
Asian weaver ant larva and pupa mixture (*Oecophylla smaragdina*)	FFGT, LSRVP (Anti-ACE) CTKKHKPNC (Antioxidant)	SGD (Pepsin and trypsin)	• UF • GFC • RP-HPLC	• LC-MS/MS	[18]
Silkworm pupa (*Bombyx mori*)	AAEYPA, AKPGVY (Antioxidant)	Alcalase *, papain, trypsin	• UF • RP-HPLC	• LC-MS/MS	[13]
Silkworm pupa (*Bombyx mori*)	SWFVTPF, NDVLEF (Antioxidant)	Alcalase *, Prolyve, Flavourzyme, Brewers Clarex	• RP-HPLC	• LC-MS/MS	[12]

Insect	Peptide Sequence (Validated Activity)	Enzymatic Hydrolysis	Peptide Purification Strategy	Peptide Identification	Reference
Silkworm pupa (*Bombyx mori*)	FKGPACA, SVLGTGC (Antioxidant)	Acidic protease, followed by neutral protease	• UF • GFC • RP-HPLC	• LC-MS/MS	[16]
Silkworm pupa (*Bombyx mori*)	ASL (Anti-ACE)	SGD (pepsin, trypsin, and α-chymotrypsin)	• UF • GFC • RP-HPLC	• LC-MS	[15]
Silkworm pupa (*Bombyx mori*)	GNPWM (Anti-ACE)	Neutral protease	• UF • IEC • GFC • RP-HPLC	• MALDI-MS/MS	[14]

* Enzyme generating the most active hydrolysate, which was selected for peptide purification. ACE: Angiotensin-I-converting enzyme, DPP-IV: Dipeptidyl peptidase-IV, GFC: Gel filtration chromatography, IEC: Ion exchange chromatography, LC: Liquid chromatography, MALDI: Matrix-Assisted Laser Desorption/Ionization, MS: Mass spectrometry, MS/MS: Tandem mass spectrometry, RP-HPLC: Reversed-phase High-Performance Liquid Chromatography, SGD: Simulated gastrointestinal digestion, UF: Ultrafiltration.

3. Applications in Human Health Management

A wide variety of pathological conditions, including chronic obstructive pulmonary disease (COPD), diabetes complications, obesity, and cancer, have been linked to oxidative stress [23][24][25]. As a result, the development of agents that reduce oxidative stress has piqued the interest of both academic research and the pharmaceutical industry. Many antioxidant peptides have been isolated from edible insects. Most of the examined edible insects' antioxidant capacities were investigated primarily using 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) and 2,2-diphenyl-1-picrylhydrazyl (DPPH) assays. The peptide FDPFPK is one of the most potent antioxidant peptides among those listed in **Table 2**. This synthetic peptide isolated from baked locusts (*Schistocerca gregaria*) showed strong $ABTS^{\bullet+}$ and $DPPH^{\bullet}$ scavenging capacity with IC_{50} values of 0.08 and 0.35

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Insect	Peptide/Hydrolysate	Bioactivity *	Potential Application	References
Cricket (*Gryllodes sigillatus*)	IIAPPER	• ACE inhibition: IC_{50}, 6.93 µg/mL • Lipase inhibition: IC_{50}, 49.44 µg/mL • α-Glucosidase inhibition: IC_{50}, 22.86 µg/mL • Radical scavenging activity (ABTS assay): IC_{50}, 15.62 mg/mL • Antioxidant activity (DPPH assay): IC_{50}, 1.01 mg/mL • Fe^{2+} chelating activity: IC_{50}, 0.14 mg/mL • LOX inhibition: IC_{50}, 8.21 mg/mL • COX inhibition: IC_{50}, 8.16 mg/mL	Anti-hypertension, antidiabetic, weight control, antioxidant, and anti-inflammation	[26][27]

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Insect	Peptide/Hydrolysate	Bioactivity *	Potential Application	References
2	LAPSTIK	• ACE inhibition: IC_{50}, 11.14 µg/mL • Lipase inhibition: IC_{50}, 104.95 µg/mL • α-Glucosidase inhibition: IC_{50}, 45.60 µg/mL • Radical scavenging activity (ABTS assay): IC_{50}, 15.69 mg/mL • Antioxidant activity (DPPH assay): IC_{50}, 0.66 mg/mL • Fe^{2+} chelating activity: IC_{50}, 0.456 mg/mL • LOX inhibition: IC_{50}, 12.3 mg/mL • COX inhibition: IC_{50}, 8.39 mg/mL		
3	VAPEEHPV	• ACE inhibition: IC_{50}, 18.85 µg/mL • Lipase inhibition: IC_{50}, 100.13 µg/mL • Radical scavenging activity (ABTS		

peptides obtained from Pterophylla beltrani (Bolivar & Bolivar) protein isolates. J. Asia-Pac. Entomol. 2020, 23, 756–761.

Insect	Peptide/Hydrolysate	Bioactivity *	Potential Application	References
		assay): IC_{50}, 3.49 mg/mL • Antioxidant activity (DPPH assay): IC_{50}, 0.29 mg/mL • Fe^{2+} chelating activity: IC_{50}, 0.155 mg/mL • LOX inhibition: IC_{50}, 7.56 mg/mL • COX inhibition: IC_{50}, 8.61 mg/mL		
	KVEGDLK	• ACE inhibition: IC_{50}, 3.67 µg/mL • Lipase inhibition: IC_{50}, 115.44 µg/mL • α-glucosidase inhibition: IC_{50}, 18.37 µg/mL • Radical scavenging activity (ABTS assay): IC_{50}, 2.88 mg/mL • Antioxidant activity (DPPH assay): IC_{50}, 8.73 mg/mL • Fe^{2+} chelating activity: IC_{50}, 0.122 mg/mL		

applications. Appl. Microbiol. Biotechnol. 2014, 98, 5807–5822.

Insect	Peptide/Hydrolysate	Bioactivity *	Potential Application	References
		• LOX inhibition: IC_{50}, 10.08 mg/mL • COX inhibition: IC_{50}, 8.43 mg/mL	antimicrobial	
Mealworm (*Tenebrio molitor*)		• ACE inhibition: IC_{50}, 12.09 µg/mL • Lipase inhibition: IC_{50}, 115.59 µg/mL • α-Glucosidase inhibition: IC_{50}, 20.37 µg/mL • Radical scavenging activity (ABTS assay): IC_{50}, 3.71 mg/mL		
	NYVADGLG	• Antioxidant activity (DPPH assay): IC_{50}, 0.99 mg/mL • Fe^{2+} chelating activity: IC_{50}, 0.198 mg/mL • LOX inhibition: IC_{50}, 9.27 mg/mL • COX inhibition: IC_{50}, 9.75 mg/mL		
	AAAPVAVAK	• ACE inhibition: IC_{50}, 8.31 µg/mL • Lipase inhibition: IC_{50}, 57.69 µg/mL		

induced expression of a cecropin A-melittin antimicrobial peptide gene confers antifungal resistance in transgenic tobacco. J. Exp. Bot. 2005, 56, 1685–1695.

Insect	Peptide/Hydrolysate	Bioactivity *	Potential Application	References
		• α-Glucosidase inhibition: IC_{50}, 10.92 μg/mL • Radical scavenging activity (ABTS assay): IC_{50}, 0.94 mg/mL • Antioxidant activity (DPPH assay): IC_{50}, 1.02 mg/mL • Fe^{2+} chelating activity: IC_{50}, 0.108 mg/mL • LOX inhibition: IC_{50}, 8.36 mg/mL • COX inhibition: IC_{50}, 9.02 mg/mL		
	YDDGSYKPH	• ACE inhibition: IC_{50}, 5.81 μg/mL • Lipase inhibition: IC_{50}, 117.94 μg/mL • Radical scavenging activity (ABTS assay): IC_{50}, 1.02 mg/mL • Antioxidant activity (DPPH assay): IC_{50}, 1.91 mg/mL		

Insect	Peptide/Hydrolysate	Bioactivity *	Potential Application	References
		• Fe^{2+} chelating activity: IC_{50}, 0.107 mg/mL • LOX inhibition: IC_{50}, 6.49 mg/mL • COX inhibition: IC_{50}, 8.07 mg/mL		
	AGDDAPR	• ACE inhibition: IC_{50}, 8.34 μg/mL • Lipase inhibition: IC_{50}, 77.46 μg/mL • α-glucosidase inhibition: IC_{50}, 19.47 μg/mL • Radical scavenging activity (ABTS assay): IC_{50}, 1.89 mg/mL • Antioxidant activity (DPPH assay): IC_{50}, 1.83 mg/mL • LOX inhibition: IC_{50}, 7.03 mg/mL • COX inhibition: IC_{50}, 9.01 mg/mL		
Locust (*Schistocerca gregaria*)	GKDAVIV	• ACE inhibition: IC_{50}, 12.82 μg/mL • Lipase inhibition: IC_{50}, 53.17 μg/mL		

Insect	Peptide/Hydrolysate	Bioactivity *	Potential Application	References
		• α-Glucosidase inhibition: IC_{50}, 15.94 μg/mL • Radical scavenging activity (ABTS assay): IC_{50}, 1.97 mg/mL • Antioxidant activity (DPPH assay): IC_{50}, 1.3 mg/mL • Fe^{2+} chelating activity: IC_{50}, 0.101 mg/mL • LOX inhibition: IC_{50}, 8.95 mg/mL • COX inhibition: IC_{50}, 8.91 mg/mL		
	AIGVGAIER	• ACE inhibition: IC_{50}, 14.4 μg/mL • Lipase inhibition: IC_{50}, 49.95 μg/mL • α-Glucosidase inhibition: IC_{50}, 13.04 μg/mL • Radical scavenging activity (ABTS assay): IC_{50}, 1.28 mg/mL		

Insect	Peptide/Hydrolysate	Bioactivity *	Potential Application	References
		• Antioxidant activity (DPPH assay): IC_{50}, 0.51 mg/mL • Fe^{2+} chelating activity: IC_{50}, 0.101 mg/mL • LOX inhibition: IC_{50}, 20.29 mg/mL • COX inhibition: IC_{50}, 8.96 mg/mL		
	FDPFPK	• ACE inhibition: IC_{50}, 79.25 µg/mL • Lipase inhibition: IC_{50}, 96.75 µg/mL • α-Glucosidase inhibition: IC_{50}, 5.95 µg/mL • Radical scavenging activity (ABTS assay): IC_{50}, 0.08 mg/mL • Antioxidant activity (DPPH assay): IC_{50}, 0.35 mg/mL • Fe^{2+} chelating activity: IC_{50}, 0.137 mg/mL • LOX inhibition: IC_{50}, 2.85 mg/mL		

Insect	Peptide/Hydrolysate	Bioactivity *	Potential Application	References
		• COX inhibition: IC_{50}, 7.40 mg/mL		
	YETGNGIK	• ACE inhibition: IC_{50}, 3.25 μg/mL • Lipase inhibition: IC_{50}, 94.91 μg/mL • Radical scavenging activity (ABTS assay): IC_{50}, 2.96 mg/mL • Antioxidant activity (DPPH assay): IC_{50}, 1.4 mg/mL • Fe^{2+} chelating activity: IC_{50}, 0.257 mg/mL • LOX inhibition: IC_{50}, 7.56 mg/mL • COX inhibition: IC_{50}, 8.83 mg/mL		
Silkworm pupa (*Bombyx mori*)	AAEYPA	• Radical scavenging activity (ABTS assay): IC_{50}, 70.32 μg/mL • Antioxidant activity (DPPH assay): IC_{50}, 70.83 μg/mL	Antioxidant	[13]
	AKPGVY	• Radical scavenging activity (ABTS		

Insect	Peptide/Hydrolysate	Bioactivity *	Potential Application	References
		assay): IC_{50}, 34.32 μg/mL • Antioxidant activity (DPPH assay): IC_{50}, 58.50 μg/mL		
Silkworm pupa (*Bombyx mori*)	SWFVTPF NDVLFF	• Antioxidant activity in AAPH induced HepG2 cells: 36.96% • Antioxidant activity in AAPH induced HepG2 cells: 30.43%	Antioxidant	[12]
Silkworm pupa (*Bombyx mori*)	FKGPACA SVLGTGC	• Radical scavenging activity (ABTS assay): IC_{50}, 0.312 mM • Radical scavenging activity (ABTS assay): IC_{50}, 0.181 mM	Antioxidant	[16]
Silkworm pupa (*Bombyx mori*)	ASL	• ACE inhibition IC_{50}, 102.15 μM	Anti-hypertension	[15]
Silkworm pupa (*Bombyx mori*)	GNPWM WW	• ACE inhibition: IC_{50}, 21.70 μM • ACE inhibition: IC_{50}, 10.76 μM	Anti-hypertension	[14]

Insect	Peptide/Hydrolysate	Bioactivity *	Potential Application	References
Silkworm pupa (*Bombyx mori*)	PNPNTN	• Promoted Concanavalin A-induced splenocyte proliferation at 100 µg/mL	Immunomodulation	[29]
Asian weaver ant (*Oecophylla smaragdina*)	FFGT LSRVP	• ACE inhibition: IC_{50}, 19.5 µg/mL • ACE inhibition: IC_{50}, 52.7 µg/mL	Anti-hypertension	[18]
	CTKKHKPNC	• Radical scavenging activity (ABTS assay): IC_{50}, 38.4 µg/mL • Antioxidant activity (DPPH assay): IC_{50}, 48.2 µg/mL	Antioxidant	
Mealworm (*Tenebrio molitor*)	LPDQWDWR APPDGGFWEWGD	• DPP-IV inhibition: IC_{50}: 0.15 mg/mL • DPP-IV inhibition: IC_{50}: 1.03 mg/mL	Antidiabetic	[22]
Larva of the Japanese rhinoceros beetle (*Allomyrina dichotoma*)	EIAQDFKTDL	In vivo model: HFD mouse model • Reduction in body weight, TG, TC, LDL/VLDL, glucose, ALT, and AST levels. • Increased HDL level compared to	Anti-obesity, weight control	[20]

Insect	Peptide/Hydrolysate	Bioactivity *	Potential Application	References
		HFD vehicle control. In vitro model: 3T3-L1 cells • Lipid accumulation assay: 30.22% of control (lowest among the identified peptides)		
Larva of the Japanese rhinoceros beetle (*Allomyrina dichotoma*)	AGLQFPVGR	In vivo model: HFD mouse model • Inhibited fat deposition in the liver of HFD mouse • Restored SOD, GPx, and GR gene expression levels, improving antioxidant capacity of liver cells.	Anti-obesity, weight control, hepatoprotective	[19]
Cotton leafworm (*Spodoptera littoralis*)	VF AVF	In vivo model: SHR rat model • A single oral administration of each peptide to SHR significantly reduced blood pressure.	Anti-hypertensive	[30]
Egyptian cotton leafworm (*Spodoptera littoralis*)	SGD hydrolysate	In vivo model: *Caenorhabditis elegans* • ORAC: IC_{50}, 0.052 mg/mL	Antioxidant	[34][35] [28][36] [37][38] [39]

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Despite the available data on the antimicrobial effects of insect-derived bioactive peptides, studies in livestock mainly investigated the effects of bioactive peptides derived from sources other than insects [34][35]. Beneficial effects of AMPs from various sources on health and performance have been shown, e.g., in poultry [40][41] and pigs

Insect	Peptide/Hydrolysate	Bioactivity *	Potential Application	References
	[46]	• Radical scavenging activity (ABTS assay): IC_{50}, 0.24 mg/mL [47] • Cellular antioxidant activity was similar to ascorbic acid (positive control) • Protective effect in vivo against acute oxidative stress		
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Cricket (*Gryllodes sigillatus*)	Cationic peptide fraction from sequential alcalase and SGD hydrolysates	• ACE inhibition: IC_{50}, 1.922 µg/mL • α-amylase inhibition: IC_{50}, 96.75 µg/mL • α-Glucosidase inhibition: IC_{50}, 13.902 µg/mL	Antidiabetic and anti-hypertension	[31]
Yellow mealworms (*Tenebrio molitor*)	RP-HPLC fraction of pepsin and trypsin hydrolysate	• Antithrombotic activity at 0.2 mg/mL: approximately 30% [50][51]	Antithrombotic	[32]
Mexican katydid (*Pterophylla beltrani*)	SGD hydrolysate	• ACE inhibition: IC_{50}, 0.49 mg/mL	Anti-hypertension	[33]
	<3 kDa fraction of SGD hydrolysate	• ACE inhibition: IC_{50}, 1.44 mg/mL • α-amylase inhibition: IC_{50}, 0.68	Antidiabetic, Anti-hypertension, [52]	

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s section, cecropin was also found to be functional against both phytopathogenic bacteria and fungi [53]. Other AMPs which can target plant pathogens with different modes of action, such as sarcotoxin, attacins, defensins, and metchnikowin, were isolated from various insects. However, these AMPs displayed broad-spectrum activities

Insect	Peptide/Hydrolysate	Bioactivity *	Potential Application	References
		mg/mL		
[54]				

* All bioactivities were results obtained from in vitro models unless otherwise stated. AAPH: 2,2′-Azobis(2-amidinopropane) dihydrochloride, ABTS: 2,2′-Azino-bis(3-ethylbenzothiazoline-6-sulfonic acid), ACE: Angiotensin-converting enzyme, COX: Cyclooxygenase, DPPH: 2,2-Diphenyl-1-picrylhydrazyl, DPP-IV: Dipeptidyl peptidase IV, GPx: Glutathione peroxidase, GR: Glucocorticoid receptor, HDL: High-density lipoprotein cholesterol, HFD: High-fat diet, LDL: Low-density lipoprotein cholesterol, LOX: Lipoxygenases, ORAC: Oxygen radical antioxidant capacity, SGD: Simulated gastrointestinal digestion, SHR: Spontaneously hypertensive rat, SOD: Superoxide dismutase, TC: Total cholesterol, TG: Triglycerides, VLDL: Very low-density lipoprotein cholesterol.

The creation of transgenic plants expressing insect AMPs to resist bacterial and fungal infections is widely implemented in the agricultural sector. The gene coding for the apidaecins, AMPs from honeybees, was genetically engineered into the genome of the potato plant. The transgenic potato demonstrated resistance to infections from plant pathogens of the *Erwinia* genus and *Agrobacterium* species [55]. In addition, a tomato plant expressing cecropin was shown to resist wilt and spot diseases caused by the pathogenic bacteria *Ralstonia solanacearum* and *Xanthomonas campestris*, respectively [56]. The fusion of two or more AMPs to form chimeric AMPs prior to transformation into plants was reported to increase the potency of the recombinant peptides to overcome future infections [57][58]. Nevertheless, the production of foreign AMP genes within the host could interfere with the plant's own gene expression system, which may indirectly affect the plant's physiology and fitness [45].

There are also insect-derived neuropeptides that could confer plants with insecticidal properties against herbivorous insects. These neuropeptides generally modulate the insect's behavior and physiology by interfering with the arthropod's developmental processes, which include reproduction, energy metabolism, and growth [59]. The injection of the neuropeptide Allatostatin Manse-AST from the tobacco hornworm (*Manduca sexta*) into the larvae of the tomato moth (*Lacanobia oleracea*) led to reduced feeding, growth retardation, and a higher mortality rate of up to 80% [60]. This neuropeptide is made up of the sequence pEVRFRQCYFNPISCF-OH [61]; it can inhibit foregut peristalsis of insect larvae, producing the aforementioned insecticidal effects [60].