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REVIEW ARTICLE

Peptides, Modern Technology for Plant Defense Response for Sustainable Green Agriculture for Increasing worldwide populations

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Abstract

Peptides are short chains of amino acids that are the building blocks of chosen proteins. Peptides are a secure and efficient alternative to existing synthetic pesticides and insecticides. A constant and reasonable food supply is critical to the foundation of economic prosperity and growth in several countries. Innovations in fertilizers, pesticides, plant breeding, trait development, and improved farming methods are the main drivers of productivity and growth. India's per capita food prices are among the lowest in the world among healthcare, pharmaceuticals, animal nutrition, and plant nutrition. In current years, peptides have become widespread research targets in crop protection as antibacterial agents, immune inducers, plant growth regulators, insecticides, and herbicides due to their rich raw material sources, excellent activity, and supreme environmental compatibility. The present manuscript briefly introduces the advances in peptide research, provides an overview of peptide research in crop protection, and summarizes the utilization of peptides in crop protection and the prospects of peptides as green pesticides for agriculture and sustainable development for increasing populations.

Keywords: Peptide; Plant Protection; Antimicrobial; Plant Growth Regulator; Insecticide

Introduction

Pesticides is a significant tool for plant protection and play a vital role in agriculture sector and food security (Zhang *et al*., 2023). Without the utilization of pesticides, there would be 78% loss in fruit production, 54% loss in vegetable production, and 32% loss in cereal production (Tudi et al., 2021). Therefore, pesticides contribute to increasing crop yields around the world but require updating to meet agricultural development needs and environmental safety requirements. In the era of organic agriculture with an emphasis on sustainable development, there is an urgent need for effective and environmentally friendly green pesticides that are effective against pests while posing a low risk to non-target organisms. As of late, peptides arose as a rising new star in the field of plant protection because of the wide accessibility of natural substance (Mita and Sato 2019; Hedges and Ryan 2020; Troyano *et al*., 2021; Patel *et al*., 2024) excellent activity (Wang *et al*., 2021) and ideal environmental compatibility (Bomgardner 2017; Zhou *et al*., 2022; Tang *et al*., 2023). They have been applied as antimicrobials and immune inducers, plant growth regulators, insecticides, and herbicides to protect plants from bacteria, viruses, pests, and weeds. Currently 18 peptides have been commercialized as green agriculture for plant protection.

The bioinsecticide Spear®, derived from a neuropeptide of spider toxin (the Blue Mountains funnel-web spider bug), won the Presidential Green Science Challenge Award in 2020 and Best New Biological Agent Award in 2021 in the US. Peptides with excellent quality and success stories, such as Spear®, are considered important new technology for crop protection and are therefore very attractive for green pesticide research and development. Understanding the studies and uses of current peptides is necessary for the development of novel peptide insecticides. Pesticides, important crop protection tools, play an important role in agriculture and food security. Production use of pesticides, fruit, vegetable, and grains production would be dramatically reduced. Therefore, pesticides contribute to increasing crop yields around the world but require updating to meet agricultural development needs and environmental safety requirements.

Peptides are short-chain biomolecules composed of two to fifty amino acids connected by peptide bonds. They can also be obtained from intermediate products of protein hydrolysis. Peptides can be classified into homomers and heteromers based on their composition, with the former consisting only of amino acids and the latter containing amino acids and non-amino acids such as glycopeptides. All peptides except cyclic peptides have N-terminal (amine group) and C-terminal (carboxyl group) residues and are classified into natural peptides and artificially synthesized peptides depending on their origin. Most natural peptides are derived from animals, plants, and microorganisms. Natural and synthetic peptides can be produced by chemical synthesis, biological fermentation, genetic recombination, and other methods. Peptides are ubiquitous in living organisms and regulate many physiological processes, making them common subjects of research in medicine, cosmetics, agriculture, and more. This article briefly introduces the advances in peptide research, reviews peptides in crop protection, and summarizes the applications of peptides in crop protection for sustainable agriculture. Peptides are a useful tool for sustainable agriculture since they are safe for the environment, effective, and have multiple applications in plant protection.

Utilization of Green Peptides in Plant Protection for Sustainable Agriculture

Peptides are advantageous for effective and environmentally friendly pest management in sustainable agriculture. They are employed as insecticides, herbicides, growth regulators, inducers of plant immunity, and antibacterials. Figure 1 illustrates the accomplishments in the history of peptide development.

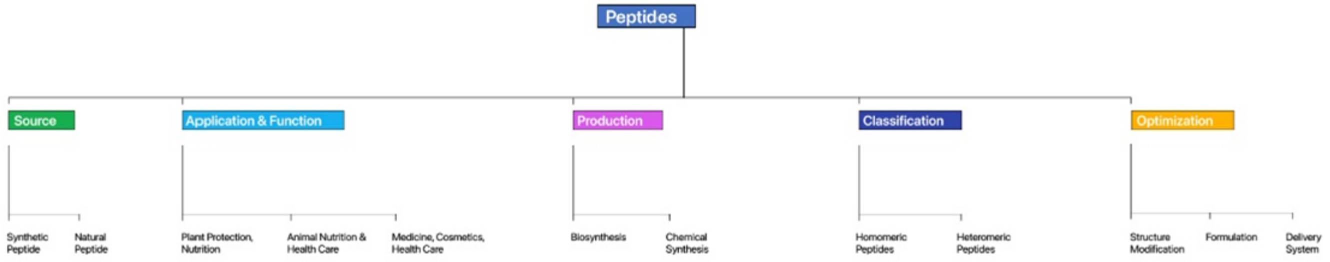

Figure1: Diagrammatic Skeleton of Peptide Research on sources, Classification, Optimization, Production, Application

Antimicrobial and Immune-inducing Peptides for Agriculture Applications

Plant pathogens attack crops and have serious negative effects on their growth and development. Conventional chemical fungicides provide effective prevention of crop pathogens. A selection of animal antimicrobial peptides (AMPs) carrying out agricultural activities is shown in Table 1.

Table 1. Classification and Agricultural Bioactivity of Animal Antimicrobial Peptides

Peptide	Source	Function	Species effectiveness	References
Abaecin	Apis mellifera	Antibacterial	Agrobacterium tumefaciens Erwinia salicis, Pseudomonas syringae Xanthomonas campestris	Casteels et al., 1990
Apidaecins	Apis melifera	Antibacterial	A. tumefaciens, E. salicis, P. syringae Rhizobium meliloti	Casteels et al., 1989, Casteels et al., 1994
Cecropin B	Hyalophora cecropia	Antibacterial, Antifungal	P. syringae pv. Tomato, P. syringae pv. Syringae, P. syringae pv. Tabaci X. campestris pv. Vesicatoria, Clavibacter michiganensis subsp. Michiganensis, Erwinia carotovora subsp. Carotovora, E. carotovora subsp. Chrysanthemi, A. tumefaciens, Penicillium digitatum Phytophthora infestans	Alan and Earle 2002
Dermaseptin	Rhacophorus	Antibacterial	Xylella fastidiosa	Kuzina et al., 2006
Drosomycin	Drosophila melanogaster	Antifungal	Botrytis cinerea, Fusarium culmorum F. oxysporum, Nectria haematococca Alternaria brassicola, A. longipes Trichoderma viride, Ascochyta pisi	Fehlbaum et al., 1994
Indolicidin	Bovine	Antibacterial	X. fastidiosa	Kuzina et al., 2006
LfcinB	Bovine	Antifungal	P. digitatum., P. Italicum, P. expansum, Penicillium sp. Alternaria sp., Aspergillus nidulans B. cinerea, F. oxysporum	Mun-oz et al., 2006
Magainin II	Xenopus laevis	Antibacterial, Antifungal	P. syringae pv. Tomato P. syringae pv. Syringae P. syringae pv. Tabaci X. campestris pv. Vesicatoria C. michiganensis subsp. Michiganensis P. digitatum X. fastidiosa	Alan and Earle, 2002
Penetratin	Drosophilid	Antibacterial	Bacillus megaterium	Palm et al., 2006
PGQ	X. laevis	Antibacterial	X. fastidiosa	Kuzina et al., 2006
pVEC	Mammalian	Antibacterial	B. megaterium	Palm et al., 2006
Spodopsin Ia	Spodoptera litura	Antibacterial	B. megaterium	Choi et al., 1997

Table 2 mentioned agriculture bioactivities antimicrobial peptides obtained from plants. Classification and agricultural bioactivity of microbes and some other antimicrobial peptides describe in table 3 and 4. Synthetic peptides accounted for 49. 33% of all peptides listed, followed by his AMPs derived from plants (29.33%), animals (16.00%), and microorganisms (5.33%). Microbial and some other sources of important bioactive antimicrobial peptides carrying out agriculture activities are shown in Tables 3 and 4. Natural AMPs are produced by animals, plants, and microbes (Sharma *et al*., 2000; Li et al., 2021a).

Table 2. Classification and Agricultural Bioactivity of Plants Antimicrobial Peptides

Peptide	Source	Function	Species Effectiveness	References
α1-purothionin	Triticum aestivum	Antibacterial	Xanthomonas Erwinia	Caleya et al., 1972
BLAD	Lupinus albus	Antifungal	B. cinerea Erysiphales	Pinheiro et al., 2018
Ca-AFP	Capsicum annuum	Antifungal	F. oxysporum Phytophthora capsici	Capella et al., 2001
Ca-LTP1	C. annuum L.	Antifungal	F. oxysporum Colletotrichum lindemuthianum	Cruz et al., 2010
J1	C. annuum	Antifungal	C. gloeosporioide , C. musae F. oxysporum	Diz et al., 2006; Seo et al., 2014
maSAMP	Citrus australasica F. Muell	Antibacterial	Liberobacter asianticum Jagoueix	Wang et al, 2021
NaD1	Nicotiana alata	Antibacterial, Antifungal	B. cinerea, F. oxysporum F. oxysporum f. Sp. vasinfectum Thielaviopsis basicola Verticillium dahlia A. nidulans, F. graminearum	Van der et al., 2008; Van der et al., 2010. Kerenga et al., 2019
Pa-AFP1	Passiflora alata Curtis	Antifungal	C. gloeosporioide	Ribeiro et al., 2011
Pe-AFP1	Passiflora edulis	Antifungal	A. fumigatus, F. oxysporum	Pelegrini et al., 2006
Peptide-1	Oryza sativa	Antifungal	Magnaporthe oryzae	Sagehashi et al., 2017
Pf2	Passiflora edulis f. Flavicarpa	Antifungal	F. oxysporum C. musae C. lindemuthianum	Agizzio et al., 2003
PhD1	Petunia hybrida	Antifungal	B. cinerea F. oxysporum	Lay et al., 2003; Segonzac and Monaghan 2019
PhD2	P. hybrida	Antifungal	B. cinerea	Lay et al., 2003. Jenssen et al., 2006
PvD1	Phaseolus vulgaris	Antifungal	F. oxysporum F. solani, F. laterithium	Mello et al., 2011
SD2	Helianthus annuus	Antifungal	Sclerotinia sclerotiorum	Urdangarin et al., 2000
Snakin-1	Solanum tuberosum	Antibacterial, Antifungal	B. cinerea, F. solani F. culmorum, F. oxysporum Plectosphaerella cucumerina Colletotrichum lagenarium C. graminicola, Bipolaris maydis A. flavus, C. michiganensis, Ralstonia solanacearum	Segura et al., 1999; Berrocal-Lobo et al., 2002

Snakin-2	S. tuberosum	Antibacterial, Antifungal	C. michiganensis R. solanacearum (rfa-) R. meliloti, B. Cinerea, F. Solani, F. culmorum, F. oxysporum f. Sp. Conglutinans, F. oxysporum f. Sp. Lycopersici, P. Cucumerina, C. graminicola, C. lagenarium, B. maydis, A. flavus	Berrocal-Lobo et al., 2002
Snakin-Z	Ziziphus jujuba	Antifungal	Pythium ultimum, A. niger	Daneshmand and Gill 2013
Thi2.1	Arabidopsis thaliana	Antifungal	F. oxysporum	Epple et al., 1995
Tn-AFP1	Coconut water Trapa natans	Antifungal	F. oxysporum, Mycosphaerella arachidicola	Wang and Ng 2005
ZmD32	Zea mays	Antibacterial, Antifungal	F. graminearum	Kerenga et al., 2019
ZmPep1	Z. mays	Antifungal	Helminthosporium, Pythium spp. Fusarium	Huffaker et al., 2011

Cathelicidins and defensins represent two major AMP families in mammals (Ouellette *et al*., 2006). Based on their sequence and structure, plant AMPs are commonly referred to as thionins, defensins, and hevein type peptides, knottins, stability-like peptides, lipid transfer proteins, snakins and cyclotides (Li *et al.,* 2021b). Bacteria and fungi are also his own AMP reservoirs (Huan *et al*., 2020). AMPs from bacteria are not produced to prevent infection, but as a competitive strategy to kill other microbes present in the body. Food and food compete for the same ecological niche, ensuring the survival of a single bacterial cell (Jenssen et al., 2006).

Synthetic peptides can be synthesized using chemical methods and screened from combinatorial libraries like bacterial two-hybrid system screening peptide library (Xu et al., 2019b), yeast-based two-hybrid system screening peptide library (Xu et al., 2019a). Hybrid libraries, (Colombo et al., 2020) and phage display (Lee *et al*., 2019) are based on affinity and specificity for key target proteins. AMPs have various inhibitory effects on bacteria, fungi, parasites, and viruses. Microbial NAF exhibits antimicrobial action against *Aspergillus flavus*, *Fusarium solani*, and *Penicillium italicum.* Animal PVEC is active against *Bacillus megaterium*, whereas plant PhD2 is active against *B. cinerea*. *Verticillium dahlia* can be effectively combated with Synthetic Alf-AFP. Table 2 listed several AMPs in development. BLAD (Pinheiro *et al*., 2018), a peptide produced during germination of *Lupine albus*, was developed as two products. ProBlad® Verde from Sym-Agro in the USA and Problad Plus™ from Consume em Verde in Portugal. Problad Plus™ (https://www.cev.com.pt/) is a biofungicides containing 20% BLAD that acts on susceptible fungal pathogens by damaging cell walls and internal membranes.

It is effective against pathogens such as powdery mildew and gray mold, and is recommended for crops such as strawberries, grapes, tomatoes, and stone fruits. Currently, it is used to control coffee leaf rust, white mold, gray mold, powdery mildew, anthracnose, bluegrass leaf rust, leaf blight, and Rhizopus from grapes, herbs, coffee, and leafy vegetables.

Table 3. Classification and Agricultural Bioactivity of Microbe's Antimicrobial Peptides

Peptide	Source	Function	Species Effectiveness	References
AFP	Aspergillus giganteus	Antifungal	F. culmorum, F. equiseti, F. Lini, F. moniliforme, F. oxysporum, F. poae, F. Proliferatum, F. solani, F. sporotrichoides, F. vasinfectum, Magnaporthe grisea, P. infestans	Marx 2004
ANAFP	A. niger	Antifungal	A. fumigatus, A. flavus, F. oxysporum, F. solani	Marx 2004
NAF	Penicillium nalgiovense	Antifungal	A. flavus , F. solani P. italicum	Marx 2004
PAF	Penicillium chrysogenum	Antifungal	A. fumigatus, A. flavus, A. niger, B. cinerea Cochliobolus carbonum F. oxysporum, Blumeria graminis f. Sp. Hordei Puccinia recondita f. sp. tritici	Kaiserer et al., 2003; Marx 2004; Barna et al., 2008

Table 4. Classification and Agricultural Bioactivity of some other Important Antimicrobial Peptides

Peptide	Source	Function	Species effectiveness	References
α_P2	Synthesized	Antifungal	P. capsici	Lee et al., 2019
Alf- AFP	Recombinant expression	Antifungal	Verticillium dahliae	Gao et al., 2000
CAMEL	Rational designed	Antibacterial	Pectobacterium carotovorum P. chrysanthemi	Kamysz et al., 2005
Cecropin P1	Recombinant expression	Antibacterial	P. syringae Pseudomonas marginata E. carotovora	Zakharchenko et al., 2005; Yevtushenko et al., 2005
CEMA	Rational-designed	Antifungal	F. solani	Yevtushenko et al., 2005
Dm-AMP1	Recombinant expression	Antifungal	B. cinerea Verticillium alboatrum	Turrini et al., 2004
DS01-THA	Rational designed	Antifungal	Phakopsora pachyrhizi	Duman-Scheel 2019; Schwinges et al., 2019
D4E1	Rational-designed	Antibacterial, Antifungal	Colletotrichum destructivum A. tumefaciens Xanthomonas populi	Cary et al., 2000; Rajasekaran et al., 2005 Vila-Perello et al., 2003
D32R	Rational-designed	Antibacterial, Antifungal	F. oxysporum, P. cucumerina B. cinerea, X. campestris pv. Translucens, C. michiganensis	Vila-Perello et al., 2003
ESF12	Rational-designed	Antifungal	Septoria musiva	Liang et al., 2002
Iseganan	Rational-designed	Antibacterial	P. carotovorum, P. chrysanthemi	Kamysz et al., 2005
KYE28	Rational-designed	Antibacterial	X. vesicatoria X. oryzae	Datta et al., 2016 Huang et al., 1997; Liu et al., 2001
MB39	Rational-designed	Antibacterial	P. syringae Erwinia amylovora	Schaefer et al., 2005

Mj- AMP1	Recombinant expression	Antifungal	Alternaria solani	Schaefer et al., 2005
MSI-99	Rational-designed	Antibacterial, Antifungal	F. oxysporum, Mycosphaerella musicola, P. syringae pv. Tomato P. syringae pv. Syringae P. syringae pv. Tabaci, X. campestris pv. Vesicatoria C. michiganensis subsp. Michiganensis, E. carotovora subsp. Carotovora, E. carotovora subsp. Chrysanthemi, A. tumefaciens, P. digitatum	Chakrabarti et al., 2003; Alan et al., 2004; Mun-oz et al., 2006 Osusky et al., 2000
MSrA1	Rational-designed	Antibacterial, Antifungal	E. carotovora Phytophthora cactorum F. solani	Osusky et al., 2005; Yevtushenko and Misra 2007
MsrA2	Rational-designed	Antibacterial, Antifungal	E. carotovora, Pythium irregulare P. paroecandrum, F. Solani, Rhizoctonia, Phytophthora P. sp. f. oxysporum, A. Alternata, B. cinerea, P. carotovorum	Osusky et al., 2004
MsrA3	Rational designed	Antibacterial, Antifungal	E. carotovora P. infestans Phytophthora erythroseptica	Osusky et al., 2004
Myp30	Rational designed	Antibacterial, Antifungal	E. carotovora Peronospora tabacina	Li et al., 2001
NCR044	Medicago truncatula	Antifungal	B. cinerea Fusarium spp.	Colombo et al., 2020
NoPv1	Peptide aptamer library	Antifungal	P. viticola P. infestans	Colombo et al., 2020
O3TR, C12O3TR	Rational designed	Antifungal	P. digitatum	Li et al., 2019
Peptaibol	Chemically modified	Antifungal	B. cinerea, Bipolaris sorokiniana F. graminearum, P. expansum	De Zotti et al., 2020
Pep11	Rational-designed	Antifungal	P. infestans	Li et al., 2019
Pexiganan	Rational designed	Antibacterial	P. carotovorum, P. chrysanthemi	Kamysz et al., 2005
PV5	Rational designed	Antibacterial, Antifungal, Antiviral	E. carotovora, TMV	Toth et al., 2020
Γ NFAP-opt,	Rationally designed	Antifungal	C.herbarum	Toth et al., 2020
Γ NFAP-optGZ SB-37	Rational designed	Antibacterial	E. carotovora	Arce et al., 1999
Shiva-1	Rational designed	Antibacterial	Pseudomonas solanacearum E. carotovora Phytoplasma	Jaynes et al., 1993; Yi et al., 2004; Du et al., 2005
SNP-D4	Peptide aptamer library	Antifungal	M.oryzae	Xy et al., 2016; Xu et al., 2019b
Tachyplesin I	Recombinant expression	Antibacterial, Antifungal	V. dahliae	Allefs et al., 1996

TK VI	Trichoderma pseudokoningii strain SMF2	Antifungal	E. carotovora, B. cinerea F. oxysporum, Ascochyta citrulline	Shi et al., 1912; Zhao et al., 2018
VG16KRKP	Rational designed	Antibacterial	Phytophthora parasitica V. dahliae; X. oryzae	Datta et al., 2015
10 R,11 R	Rational designed	Antibacterial, Antifungal, Antiviral	X. campestris E. carotovora Fungi TMV	Bhargava et al., 2007

Immune Inducing Peptides (IIPs) for Sustainable Agriculture

Because of their function in host innate defence (HID), AMPs can act as immune inducers in plants, trigger defence signals, and enhance innate immunity (Bende et al., 2014; Bende et al., 2015). Three types of peptides have been investigated as commercial immune inducers. Invaio Sciences' peptide maSAMP (https: //www.invaio.com/) is being used to combat the destructive citrus disease. This peptide kills *Liberobacter asianticum jagoueix*, the causative agent of Huanglongbin disease, and activates the plant's immune system to prevent subsequent infections. The helical structure of maSAMP quickly penetrates bacterial membranes and lyses them within 30 minutes. Considering the lack of effective products to combat this disease, it is hoped that maSAMP can become an effective tool. This product is used as a seed treatment against Asian soybean rust. Phytotech's FLG22 (https: //phytotechlab.com/) induces a natural immune response. Its sequence is derived from the highly conserved N-terminal region of *Pseudomonas aeruginosa* flagellin. FLG22 and its derivatives induce defense responses and exhibit elicitor activity in *Lycopersicon esculentum* and *Arabidopsis thaliana*. Numerous IIPs are under development. PIP1 and PIP2 enhance immune responses and pathogen resistance in *Arabidopsis* (Hou *et al*., 2016). *Nicotiana tabacum* NbPPI1 stimulates the immune response and increases plant resistance to *Phytophthora* (Wen *et al*., 2021). The maize immune signaling peptide Zip1 reduces the virulence of the maize smut fungus (Stegmann *et al*., 2017). Cowpea and kidney bean defense causes an increase in the defense-related plant hormones salicylic acid and jasmonic acid (Schmelz et al., 2006; Schmelz et al., 2012). Treatment of plants with inceptin produces volatile organic molecules such as indole and methyl salicylate, which are natural enemies of armyworm moths. Therefore, it provides indirect protection.

Plant Growth Regulating Peptides (PGRPs)

PG and development are influenced by plant hormones such as auxins, cytokinins, and gibberellins that mediate intercellular communication during development. However, recent studies have shown that peptide signaling molecules (PSMs) also play important roles in various developmental processes and environmental responses in plants (Olsen *et al*., 2002; Ryan *et al*., 2002; Boller 2005; Germain *et al*., 2006; Matsubayashi and Sakagami 2006; Farrokhi *et al*., 2008; Hou *et al*., 2014). PGRPs are a new class of plant hormones (Matsubayashi and Sakagami, 2006) with signaling properties and hormonal actions. They exhibit significant biological activity at very low concentrations (10-7-10-9 M). These findings highlight the importance of peptides in regulating plant growth. Approximately 30 families of peptide phytohormones have been identified in plants, and many more interact with plants, including bacterial and fungal pathogens, plant-parasitic nematodes, and symbiotic and plant beneficial bacteria and fungi. It exists in a variety of living things (Dodueva *et al*., 2021). Classes of plant hormones (CLE, CEP, RALF, IDA, PSK, PSY, and PEP) have been found in bacteria, fungi, and nematodes that interact with plants (Dodueva *et al*., 2021). These peptide precursors are processed into mature peptides in plants, which then interact. It binds to plant receptors and activates downstream signaling pathways, triggering growth responses. Peptides that are effective in regulating PG are listed in table 5, 6 and 7, along with their functions in plants. Functions Peptides and their functions as Plant Growth Regulators are mentioned in table 8. The sources of these PGRPs are showing that plant peptides account for 58.93%, followed by synthetic 19. 64%, microbial 14. 29%, and animals 7.14%.

Table 5. PGR Peptides for Animal and their Functions as Plant Growth Regulators

Peptide	Source	Function	References
CLE	Heterodera spp, Globodera spp, Rotylenchulus spp. Meloidogyne spp.16D10 Meloidogyne spp. MAP	Activate downstream signaling pathway leading to growth response	Dodueva *et al*., 2021
CEP	*Rotylenchulus* spp. Meloidogyne spp.	Activate downstream signaling pathway leading to growth response	Dodueva *et al*., 2021
Hicure®	Animal protein hydrolysates	Improve plant quality and enhance resistance to environmental stresses	Carillo *et al*., 2022
IDA	*Meloidogyne* spp.	Activate downstream signaling pathway leading to growth response	Dodueva *et al*., 2021

Table 6. PGR Peptides for Plants and their Functions as Plant Growth Regulators

Peptide	Source	Function	References
AtRALF1	A. thaliana	Overexpression causes semi-dwarfism, exogenous peptide	Haruta et al., 2008; Mingossi et al., 2010
AtRALF23	A. thaliana	Overexpression impairs brassinolide-induced hypocotyl elongation and causes semi-dwarfism	Srivastava et al., 2009
CEPs	A. thaliana	N-demand signaling, lateral growth, nodulation	Yoshii et al., 2014; Mohd-Radzam et al., 2016
CIFs	A. thaliana	Casparian strip formation	Doblas et al., 2017; Nakayama et al., 2017
CLE19	A. thaliana	Root apical meristem size	Nakayama et al., 2017
CLE25	A. thaliana	Improvement of ABA level	Takahashi et al., 2018
CLE41/44 (TDIF)	A. thaliana	Inhibition of xylem differentiation	Fisher and Turner 2007; Hirakawa et al., 2008
CLE40	A. thaliana	Cell differentiation	Stahl et al., 2013; Nikonorova et al., 2018
CLV3, CLE2	A. thaliana	Stem cell renewal and differentiation	Clark et al., 1993; Kayes and Clark 1998; DeYoung et al., 2006; Muller et al., 2008;

			Kinoshita et al., 2010; Hu et al., 2018
EPF2	A. thaliana	Stomata development	Lee et al., 2015
GmCLE40	A. thaliana	Stem cell differentiation	Stuhrwohldt and Schaller 2019
GRI	A. thaliana	Cell death control	Wrzaczek et al., 2015
IDA	A. thaliana	Floral organ abscission	Cho et al., 2008; Stenvik et al., 2008; Santiago et al., 2016
LRPP	Plants	Improve the resistance to environmental stresses	https://www.hello-nature.com/us/
MtCLE12	A. thaliana	Regulation of nodulation	Kassaw et al., 2017
MtRALFL1	Medicago trunculata	Overexpression causes reduced number and abnormal nodule development, regulated by bacterial nod factors	Combier et al., 2008
NaRALF	Nicotiana attenuata	RNAi downregulation causes long roots, abnormal root hairs	Wu et al., 2007
Phytosulfokine (PSK)	A. thaliana	Root and hypocotyl cell elongation	Matsubayashi et al., 2002; Matsubayashi et al., 2010; Wang et al., 2015
PSY	A. thaliana	Cell proliferation and expansion	Amano et al., 2007; Fuglsang et al., 2014
PtdRALF1, PtdRALF2	Hybrid Populus	Exogenous peptide causes alkalinisation of cell culture growth medium	Haruta and Constabel, 2003
RALF1	A. thaliana	Extracellular alkalinisation	Haruta et al., 2014
RALF23	A. thaliana	Extracellular alkalinisation	Stegmann et al., 2017
RGFs	A. thaliana	Root meristem activity, gravitropsism	Hidefumi et al., 2016; Ou et al., 2016; Song et al., 2016
SacRALF1	Saccharum spp	Exogenous peptide causes inhibition of microcalli development	Mingossi et al., 2010
SlPRALF	Solanum lycopersicum	Exogenous peptide causes inhibition of pollen tube growth	Covey et al., 2010
SlRALF	Solanum lycopersicum	Exogenous peptide causes alkalinisation of growth medium and inhibition of tomato and Arabidopsis root growth	Pearce et al., 2001
Systemin	A. thaliana	Wound response	Wang et al., 2018

TobHypSys, TomHypSy	A. thaliana	Defence signaling	Stuhrwohldt and Schaller 2019
Tomato CLV3	A. thaliana	Stem cell renewal	Cao et al., 2015

Table 7. PGR Peptides for Microorganisms and their Functions as Plant Growth Regulators

Peptide	Source	Function	References
CLE	Actinobacteria sp. Thiotrichales sp. Acidimicrobiaceae sp. Gemmatimonadetes sp. Actinobacteria sp. Rhizophagus irregularis, R. diaphanous R. cerebriforme, R. clarus	Mimic peptide phytohormones	Dodueva et al., 2021
CEP	Ralstonia syzygii	Mimic peptide phytohormones	Dodueva et al., 2021
Eapeptide 91,938	E. amylovora	Stimulate crop growth and enhance defense ability and stress resistance	https://www.planthealthcare.com/
IDA	Elampsora larici-populina Colletotrichum fructicola	Mimic peptide phytohormones	Dodueva et al., 2021
PEP	Metschnikowia sp. JCM33374 Mycolicibacterium conceptionense	Mimic peptide phytohormones	Dodueva et al., 2021
PSK	Tilletia sp., Diplodia sp. Macrophomina phaseolina Cercospora sp., Pseudocercospora sp. Zymosentoria spo Proteobacteria s	Mimic peptide phytohormones	Dodueva et al., 2021
PSY	X. oryzae pv. Oryza other Xanthomonas species	Mimic peptide phytohormones	Dodueva et al., 2021
RALF	F. oxysporum Other 26 fungal species Stretomyces acidiscabies and 8 species of Actinobacteria	Extracellular alkalinisation	Dodueva et al., 2021

Plant growth regulating peptide (GRP) has a wide range of functions in PG and development. For example, the functional peptide PY91, discovered by TIBO Crop Science in 2021, disrupts plant growth. CLAVATA3 peptide regulates meristem size (Lay and Anderson 2005). The S cysteine-rich (SCR) peptide is a self-incompatibility recognition factor in Brassicaceae pollen (Fletcher *et al*., 1999). RALF is a family of peptides that play a key role in plant cell growth (Okuda *et al*., 2009). The root derived CLE25 peptide allows plants to cope with self-incompatibility. Cope with drought stress by regulating the expression of NCED (Takahashi *et al*., 2018; Mita and Sato 2019). NCED increases abscisic acid (ABA) levels (Endo *et al*., 2008; Seo *et al*., 2000) to induce stomatal closure and maintain water balance. The effects of traditional plant hormones can be amplified or deactivated using peptide-based hormone products. CLE41/TDIF, BR peptide, and auxin jointly control root formation. In contrast, CLE27 expression is inhibited by auxin. Four types of peptides are used as commercially available plant growth regulators (PGRs). The plant peptide LRPP (https: //www.hello-natur e.com/us/) is also a biostimulant that is the active ingredient in the commercial product Tandem developed by the Italian company Hello Nature. It is a powerful biostimulant that improves tolerance to environmental stresses such as drought, low and high temperatures, or poor soils. This product is used during the sowing stage to establish a closer and mutually beneficial relationship with the seeds. As a growth regulator, it protects against fungi, bacterial pathogens, and nematodes by stimulating growth, the plant's natural defenses and metabolism. Recommended uses include seed treatments and foliar applications. Hicure® (https: //www.syngenta.com/en) is a natural biostimulant with excellent potency and flexibility, containing easily absorbed peptides and amino acids, which enhances the quality of botanicals. It has been proven to improve and increase resistance to environmental stress. The product is applied as a conventional spray or macerating solution for best results during critical developmental stages, before replanting or transplanting, environmental stress, or before transportation.

Table 8. Other PGR Peptides and their Functions as Plant Growth Regulators

Peptide	Source	Function	References
CAMEL	Rational designed	Inhibiting the growth of different species of Pectobacterium	Kamysz *et al.*, 2005
CEP1	Rational designed	Increases nutrient uptake rates along plant roots	Roy *et al.*, 2022
KEYLAN Ca	Rational designed	Optimizing Calcium uptake and boosting plant metabolism	https://www.hello-nature.com/us/
KEYLAN Combi	Rational designed	Optimizing nutrient uptake and boosting plant metabolism	https://www.hello-nature.com/us/
KEYLAN Fe	Rational designed	Optimizing Iron uptake and boosting plant metabolism	https://www.hello-nature.com/us/
KEYLAN Fe	Rational designed	Optimizing Iron uptake and boosting plant metabolism	https://www.hello-nature.com/us/
KEYLAN Max	Rational designed	Optimizing nutrient uptake and boosting plant metabolism	https://www.hello-nature.com/us/
KEYLAN Mn	Rational designed	Optimizing Manganese uptake and boosting plant metabolism	https://www.hello-nature.com/us/
KEYLAN Zn	Rational designed	Optimizing Zinc uptake and boosting plant metabolism	https://www.hello-nature.com/us/
NOP-1	Rational designed	Inhibiting plant senescence	Hofmann *et al.*, 2021
PEP6-32	Rational designed	Plant seedlings presented longer hypocotyls and diminished cotyledon expansion when grown under red light.	Shuipys *et al.*, 2019
PSK-α	Rational designed	Promote cell growth and proliferation	Yu *et al.*, 2016

Insecticidal Peptides (ISPs)

Pest control is an important concern for agriculture, as pests can cause approximately 13-16% crop losses (Rivera-de-Torre *et al*., 2021). Pests are mainly controlled by chemical insecticides. Inappropriately, the widespread use of these products has resulted in decreased resistance to pests as well as negative effects on human health (HH) and the environment (Windley *et al*., 2012; Maienfisch and Koerber 2024). Therefore, there is a need to develop biopesticides as an alternative approach for pest control (Park *et al*., 2011). ISPs with standard properties are currently being considered as possible alternatives. ISPs act on a variety of pests, including Lepidoptera, Diptera, and Hemiptera. Some reported ISPs and their functions are summarized in Table 9-11. ISPs were mostly derived from animals (63.1%), followed by plants (19. 64%) and synthetic peptides (11%). There are very few ISPs derived from microbes, except for some fungi and bacteria, such as destruxin A (DA) secreted by *Metarhizium anisopliae* and longibrachinA-I from *Trichoderma longibrachiatum* RIFAI. Natural ISPs are mainly derived from the venoms of arthropods (spiders, scorpions, ants, etc.) and marine animals (jellyfish) (Arntzen 1972; Yu *et al*., 2005; Yu *et al*. 2021). Sea anemone (Liu *et al*., 2010; Yan *et al*., 2014) Cone snail (Bruce *et al*., 2011; Lebbe *et al*., 2014; Gao *et al*., 2017; Chen *et al*., 2018). These studies pave the way for the development of novel insect control agents based on cyclic peptidomimetics. Antagonists in the backbone of insect neuropeptides (Elakkiya *et al*., 2019). Vestaron, a recent Green Chemistry award winner, is leading the peptide-based revolution in crop protection. GS-ω/κ-HXTX-Hv1a peptide was used as the active ingredient to launch two Spear® products ((https: //www.vestaron.com/): 1) Spear® -T is effective against thrips, whiteflies, fruit flies and spider mites found in greenhouses, Spear®-Lep is effective against lepidopteran pests such as caterpillars, nematodes, and raptors in indoor and outdoor crops.

Table 9. Classification and Agricultural Bioactivity of Plants Insecticidal Peptides and their Function

Peptide	Source	Function	Species effectiveness	References
BrD1	Brassica rapa	Insecticidal	Nilaparvata lugens	Choi et al., 2009
Cter M	Clitorea ternatea	Insecticidal	H. armigera	Poth et al., 2011
CycloviolacinH3, CycloviolacinO1, CycloviolacinO2, CycloviolacinO3, CycloviolacinO8, CycloviolacinO12, CycloviolacinO13, CycloviolacinO14, CycloviolacinO15, CycloviolacinO16, CycloviolacinO19, CycloviolacinO24, CycloviolacinY1, CycloviolacinY4, CycloviolacinY5	Viola odorata	Insecticidal	M. persicae Pomacea canaliculate Trichostrongylus Colubriformis Hemonchus contortus	Colgrave et al., 2008; Plan et al., 2008; Colgrave et al., 2009

Hypa A	Hybanthus parviflorus	Insecticidal	Ceratitis capitata	Mulinari et al., 2007
JaburetoX-2Ec	Canavalia ensiformis	Insecticidal	Dysdercus peruvianus Callosobruchus maculatus S. frugiperda	Mulinari et al., 2007
KalataB1, KalataB2, KalataB6 KalataB7, KalataB	Oldenlandia affinis	Insecticidal	H. armigera P. canaliculate H. contortus T. colubriformis	Jennings et al., 2005; Plan et al., 2008. Poth et al., 2011
Parigidin-Br1	Palicourea rigida	Insecticidal	Diatraea saccharalis S. frugiperda	Pinto et al., 2012
PA1b	Pisum sativum	Insecticidal	Sitophilus oryzae S. granarius S. zeamays, Culex pipiens. A. pisum Aedes aegypti	Gressent et al., 2007; Eyraud et al., 2013; Eyraud et al., 2017
Sero-X®	C. ternatea	Insecticidal	H. armigera Bemesia tabaci Nezara viridula	Eyraud et al., 2017
Varv A, Varv E, Kalata S	V. odorata	Insecticidal	H. contortus T. colubriformis	Segonzac and Monaghan 2019
Vhl-1	V. hederacea	Insecticidal	H. contortus T. colubriformis	Colgrave et al., 2008
VrCRP	Vigna radiata	Insecticidal	Callosobruchus chinensis	Chen et al., 2002
VrD1	V. radiata	Insecticidal	Bruchidae	Liu et al., 2006

Maximum plant-based ISPs, such as cyclic peptides (CPs), *pea albumin*, defense and recombinant peptides (Grover *et al*., 2021), are derived from the Rubiaceae, Fabaceae, Violaceae, Solanaceae, and Cucurbitaceae families (Craik 2010). More than 47 CPs from *Clitoria ternatea* (Gilding *et al*., 2016) showed insecticidal effects. PA1b (*Pea albumin 1 subunit b*) is a 37 amino acid peptide isolated from the seeds of *Pisum sativum* and exhibits significant insecticidal activity against insects such as cereals beetles, *Culex mosquitoes*, and *Aedes aegypti* (Gressent *et al*., 2011). and certain species of aphids. This toxin binds to subunits c and e of the plasma membrane H-ATPase (V-ATPase) in the insect midgut (Eyraud *et al*., 2017). In 2017, Sero-X®, the world's first plant-based cyclopeptide bioinsecticide, was developed by his Innovate Ag in Australia (Muttenthaler *et al*., 2021).

Due to its non-toxic and bee-friendly properties, it is approved for use on Australian cotton and macadamia nut plants to control *Helicoverpa armigera*, *Bemesia tabaci* and *Nezara viridula*. A series of mimic peptides with favorable insecticidal activity (Horodyski *et al*., 2011; Hardy *et al*., 2013; Hou *et al*., 2014; Haruta *et al*., 2014; Hidefumi *et al*., 2016; Herzig *et al*., 2016; Doblas *et al*., 2017; Heep *et al*., 2019; Fuminori *et al*., 2019; Herzig *et al*., 2020; Hofmann *et al*., 2021; He *et al*., 2021) were obtained by modifying natural peptides to overcome bio instability.

Table 10. Classification and Agricultural Bioactivity of Microbes Insecticidal Peptides and their Function

Peptide	Source	Function	Species Effectiveness	References
Beauveriolide I	Beauveria bassiana	Insecticidal	S. litura C. chinensis	Mochizuki et al., 1993
Cyclic depsipeptides	Marine fungi	Insecticidal	S. litura C. chinensis	Wang et al., 2018
Cyclodipeptides	Marine fungi	Insecticidal	Helicoverpa zea	Wang et al., 2017
Destruxins	Metarhizium anisopliae	Insecticidal	Lepidoptera Homoptera Diptera Orthoptera	Hu et al., 2004
Iso-isariin D	B. bassiana	Insecticidal	Artemia salina	Hu et al., 2004
Longibrachin A-I, Longibrachin A–II–b	Trichoderma longibrachiatum RIFAI	Insecticidal	Calliphora vomitoria	Du et al., 2014
Pumilacidin C	Marine bacteria	Insecticidal	A. aegypti	Moreira et al., 2022
SLP1	Streptomyces laindensis H008	Insecticidal	Lipaphis erysimi	Xu et al., 2016

Table 11. Classification and Agricultural Bioactivity of some Others Insecticidal Peptides and their Function

Peptide	Source	Function	Species Effectiveness	References
CAPA-PK analogue (1895 þ 2315)	CAPA-PK analogue	Insecticidal	*M. persicae*	Shi *et al*., 2022
GS-ω/κ-HXTX-Hv1a	Genetic engineering	Insecticidal	*Aphid Hrips, Delphacidae*	Bomgardner 2017
H17	Allatostatin mimic	Insecticidal	*D. punctata*	Kai *et al*., 2009
K-Aib-1	Kinin mimic	Insecticidal	*A. pisum*	Smagghe *et al*., 2010
K15, K24, P5, B1, II12, A6 Insecticidal	Allatostatin mimic	Insecticidal	*D. punctata*	Kai *et al*., 2010; Wang *et al*., 2018; Wang *et al*., 2019
Manse-AT	Allatotropin	Insecticidal	*M. sexta*	Horodyski *et al*., 2011
Manse-AT (10–13)	Allatotropin	Insecticidal	*M. sexta*	Kai *et al*., 2018
PPK-Jo Insecticidal	Kinin analogues	Insecticidal	*Moths*	Kaczmarek *et al*., 2021
II-1, IV-3, M1, L25, L7	Kinin mimic	Insecticidal	*Aphis glycines*	Zhou *et al*., 2006; Zhang *et al*., 2015; Zhang *et al*., 2020; Zhou *et al*., 2022
2460 analogue	Kinin analogues	Insecticidal	*M. persicae*	Shi *et al*., 2022
1963 analogue	Diapause hormone analogue	Insecticidal	*H. zea*	Reynolds *et al*., 2019

By introducing unnatural amino acids into the enzyme site, several insect kinin mimetics have been obtained that produce products that are significantly resistant to enzymatic degradation (Nachman *et al*., 2002). Zhou *et al.* (2022) recently discovered insect kinin analogs L25 and M1 with excellent aphicidal activity and low toxicity to honeybees. The discovery of these peptide-like compounds provides a new strategy for developing new environmentally friendly insecticides.

Herbicidal Peptides (HPs)

In general, weeds cause the highest potential losses (34%) compared to pests and pathogens (18% and 16% losses). Weed control is mechanical or chemical and therefore more effective than controlling animal pests and diseases (Oerke 2006). Traditional herbicides help maintain crop yields, but the heavy reliance on herbicides has resulted in negative impacts such as residues on crops and the environment. Therefore, there is a growing need for new environmentally friendly herbicides (Shi *et al*., 2020). Tables 12 and 13 present an overview of the functions and classifications of various herbicidal peptides. They are mainly derived from microbes (43.75%), followed by plants (37.50%), and synthetic substances (18.75%). Natural and synthetic peptides are considered promising herbicides for crop protection applications. Bialaphos is a tripeptide isolated and purified from the fermentation broth of *Streptomyces hygroscopicus* (Shi *et al*., 2020). Thamatomin A is derived from *Streptomyces acidiscabies*. Several herbicidal peptides are found in plants, such as five dipeptides and one pentapeptide from corn gluten meal hydrolysate (Liu and Christians 1996; Unruh *et al*., 1997). As shown in Tables 12 and 13, these peptides are effective against a variety of weeds. For example, Romidepsin is active against *Amaranthus palmeri L.* and *Sinapsis arvensis L*. Ala-Ala is active against *Lolium perenne L*. Tentoxin, a cyclic tetrapeptide from *Alternaria tenuis*, inhibits cyclic photosynthetic phosphorylation period and energy transfer, leading to chlorosis in seedlings while chlorosis had no effect on soybeans and corn. Peptides can also be used with herbicides to encourage weeds' stomata to open under unfavorable circumstances, thereby improving the weeds' ability to absorb the drug and causing them to die back more quickly. Thaxomine A, the active ingredient in Opportune™ (https://marronebio.com/) developed by Marrone Bio Innovation, is a unique cellulose synthesis inhibitor. In 2013, it was approved by the U.S. Environmental Protection Agency as a non-polluting organic herbicide for weed control in rice and other grain fields.

Table 12. Classification and Agricultural Bioactivity of Plant Herbicidal Peptides

Peptide	Source	Function	Species Effectiveness	References
Ala-Ala	Z. mays L.	Herbicidal	Lolium perenne L.	Unruh et al., 1997
Ala-Asn	Z. mays L	Herbicidal	L. perenne L.	Liu and Christians 1994
Ala-Gln	Z. mays L	Herbicidal	L. perenne L	Liu and Christians 1994
Gly-Ala	Z. mays L	Herbicidal	L. perenne L.	Liu and Christians 1994
Gln-Gln	Z. mays L	Herbicidal	L. perenne L.	Liu and Christians 1994
Leu-Ser-Pro-Ala-Gln	Z. mays L	Herbicidal	L. perenne L	Liu and Christians 1996

Table 13. Classification and Agricultural Bioactivity of Microbes Herbicidal Peptides

Peptide	Source	Function	Species effectiveness	References
AMPB-Ala-Ala-AMPB	Actinomycetes	Herbicidal	Weed	Shi et al., 2020
AMPB-Gly-Ala	Actinomycetes	Herbicidal	Weed	Shi et al., 2020
Basta	Streptomyces viridochromogenes	Herbicidal	Weed	Schwartz et al., 2004
Bialaphos	Actinomycetes	Herbicidal	weed	Shi et al., 2020
Compounds 1-7	Bacillus clausii DTM1	Herbicidal	Poa annua L	Guo et al., 2015
des-N2 - methylthaxtomin C	S. scabies	Herbicidal	Agrotis palustri	Shi et al., 2020
Herbiace	S. viridochromogenes	Herbicidal	Weed	Schwartz et al., 2004
Hydroxythaxtomin A	S. scabies	Herbicidal	Lemna minor	Shi et al., 2020
Hydroxythaxtomin C	S. scabies	Herbicidal	L. minor	Shi et al., 2020
Phosalacine	Actinomycetes	Herbicidal	Weed	Shi et al., 2020
Plumebmycin A	Actinomycetes	Herbicidal	Weed	Shi et al., 2020
Plumebmycin B	Actinomycetes	Herbicidal	Weed	Shi et al., 2020
Resormycin	Streptomyces platensis MJ953-SF5	Herbicidal	Dicotyledonous weeds	Shi et al., 2020
Romidepsin	Burkholderia rinojensis	Herbicidal	Amaranthus palmeri L. Sinapsis arvensis L., Amaranthus tuberculatus Trifolium repens L. Conyza canadensis L. Bassia scoparia L. Stellaria media (L.) Abutilon theophrasti Medik. Convolvulus arvensis L. P. annua L. Avena fatua L. Echinochloa crus-galli(L.) P. Beauv. Commelina virginica L. Setaria faberi Herrm. Cyperus dif formis L	Owens et al., 2020
Tentoxin	Alternaria tenuis	Herbicidal	weed	Arntzen 1972

Thaxtomin A	S. scabies	Herbicidal	L. minor A. palustris	Shi et al., 2020
Thaxtomin A o-isomer	S. scabies	Herbicidal	L. minor, A. palustris	Shi et al., 2020
Thaxtomin A p-isomer	S. scabies	Herbicidal	A. palustris	Shi et al., 2020
Thaxtomin B	S. scabies	Herbicidal	A. palustris	Shi et al., 2020
Thaxtomin C	S. scabies	Herbicidal	L. minor	Shi et al., 2020
Triaphos	Actinomycetes	Herbicidal	Weed	Shi et al., 2020
Compounds 14,15	Synthesis	Herbicidal	Weed	Dai and Chen 1999
Compound 5a	Synthesis	Herbicidal	Barnyard Grass Crabgras	Chen et al., 1993

Pest Resistance Peptides (PRPs)

Insects develop resistance to pesticides over time (just as disease-causing bacteria can become resistant to antibiotics), extending the effective lifespan of individual pesticides. For example, the fall armyworm, an annual corn pest that can destroy entire crops, has developed resistance to pesticides (Gutierrez-Moreno *et al*., 2019; Barber *et al*., 2023). The peptides used for controlling plant pathogens and their scale of testing are mentioned in Table 14. The development of pest resistance can be minimized with integrated pest management solutions, such as rotating different pesticides through the seasons. However, in many cases, the lack of new pesticides leaves farmers with few options.

Table 14. The Peptides used for Controlling Plant Pathogens and their Scale of Testing

Peptides	Origin	Target Pathogens	Testing Method	Testing Scale	References
Snakin-1	Potato	Clavibacter michiganensis, Botrytis cinerea	Transgenic expression	Lab scale	Segura et al., 1999
MSI-99	Synthetic	F.oxysporum, Sclerotinia sclerotiorum, A. alternata, B. cinerea	Transgenic expression	lab and Green house scale	Chakrabarti et al., 2003
Thionin	Arabidopsis thaliana	Ralstonia solanacearum, Fusarium oxysporum	Transgenic expression	Lab scale	Chan et al., 2005
NmDef02	Nicotiana megalosiphon	Peronospora hyoscyami	In-vitro killing assay, Transgenic expression	Lab, Green house and Field scale	Portieles et al., 2010
Thanatin	Podisus maculiventris	Fusarium graminearum, B. cinerea	In-vitro killing assay Foliar spray	Lab scale	Koch et al., 2012
MsrA-1	Synthetic	Phytophthora cactorum, F. solani	Transgenic expression	lab and Green house scale	Osusky et al., 2000; Rustagi et al., 2014

Cecropin A	Hyalophora cecropia	F. oxysporum, Dickeya dadantii, F. verticillioides	In-vitro killing assay, Transgenic expression	lab and Green house scale	Cavallarin et al., 1998; Bundo et al., 2014; Montesinos et al., 2016
Melittin	Apis mellifera	X. oryzae	In-vitro killing assay	Lab scale	Shi et al., 2016
Tachyplesin I	Horseshoe crab	Pectobacterium carotovorum	In-vitro killing assay, Transgenic expression	Lab scale	Lipsky et al., 2016
GTannins	Sapium baccatum	Ralstonia solanacearum	In-vitro killing assay, Foliar spray	Lab and greenhouse scale	Vu et al., 2017
BP/BPC serial peptides	Synthetic	Erwinia amylovora, X. vesicatoria, Pseudomonas syringae, F. oxysporum, Penicillium expansum, A. niger, Rhizopus stolonifer, Stemphylium vesicarium	In-vitro killing assay, Foliar spray, Transgenic expression	Lab, Green house and Field scale	Monroc et al., 2006; Badosa et al.,2007; Badosa et al., 2009; Puig et al., 2014; Puig et al., 2015; Montesinos et al., 2017; Montesinos et al., 2021
hCAP18/LL-37	Human	Pectobacterium carotovorum	In-vitro killing assay, Transgenic expression	Lab scale	Jung et al., 2012; Holaskova et al., 2018
PAF26	Synthetic	P. digitatum	In-vitro killing assay	Lab scale	Wang et al., 2018
Random peptides mixture	Synthetic	X. perforans, X. campestris	In-vitro killing assay, Foliar spray	Lab and greenhouse scale	Topman et al., 2018
alfAFP	alfalfa	Verticillium dahliae	Transgenic expression	Lab, Green house and Field scale	Gao et al., 2000
NoPv1	Synthetic	Plasmopara viticola, Phytophthora infestans	In-vitro killing assay, Foliar spray	Lab and greenhouse scale	Colombo et al., 2020
ϵ-poly-L-lysine	Synthetic	Botrytis cinerea	In-vitro killing assay, Foliar spray	Lab, Green house and Field scale	Sun et al., 2017; Shu et al., 2021
SAMP	Microcitrus australiasica	Liberibacter crescens	In-vitro Killing assay,	Lab scale	Huang et al., 2021

Ac-AMP2	Amaranthus caudatus	Penicillium expansum	Transgenic expression, Foliar spray In-vitro killing assay, Transgenic expression	Lab scale	Huang et al., 2021

Advantages of Peptide Biologics for Crop Protection

The food supply is at risk when innovation moves more slowly because pests get resistant to current pesticides. The dual challenges are that sustainability and the demand for new products are required, yet environmental safety cannot be compromised. Biologics peptide designs environmentally friendly pesticides that work as effectively as standard synthetic agrochemicals, while also resetting the resistance clock through rapid introduction of more products quickly and more safely. Biopesticides make up a small portion of the $58 billion crop protection market but are growing more than 15% per year and are expected to rival the synthetic market over the next two decades (Damalas and Koutroubas 2017). The promising potential of biologics as biopesticides has been known for several decades, but challenges in production and distribution prevented their widespread commercialization until recently. Large protein biologics such as antibodies or enzymes have driven a biotechnological revolution in the pharmaceutical industry due to their high efficacy, predictable safety, and ease of development. However, in crop protection, they are less successful as biopesticides because they generally have limited stability in the field, require a cold chain, and have difficulty penetrating the cuticle of insects to achieve essential goals. To ensure a sustainable future and move away from synthetic agricultural chemicals, these challenges must be addressed. Smaller versions of proteins called peptides can overcome this stability and transport issues and target the same receptors as synthetic pesticides. In nature, insect-specific peptide neurotoxins are used by many species of spiders, scorpions, and millipedes to immobilize and kill their prey. This provides a model for the development of safe and effective pesticides (King 2019). Other advantages include the small size of the peptides. This allows for easier passage through external barriers, allows for more efficient manufacturing, and reduces input costs for farmers. Another advantage in manufacturing and delivery is the fact that peptides can be highly stabilized by cross-linking, thus ensuring sustained field performance and stability throughout the supply chain. Stable peptides do not require a cold chain, thus removing a problematic and costly barrier to the use of biologics in crop protection. Importantly, peptide insecticides have low environmental toxicity because they are amino acid building blocks and do not contain toxic metabolites.

Because of their great selectivity for target pests and receptors, there is no chance that vertebrates or helpful insects like bees will unintentionally become harmed.

Challenges and Opportunities for a Peptide Biological Future

Three factors play a role in the widespread commercialization of peptide biopesticides: 1. Bioavailability, 2. Manufacturing cost, and 3. Regulation.

Bioavailability of Peptide

For biologics that target insect receptors, bioavailability remains a significant obstacle to their commercialization (Windley *et al*., 2012). This challenge can be conceptualized by imagining the pest's external structures such as exoskeleton or intestinal mucosa as a filter that discriminates by size. Large molecules such as proteins and nucleic acids are mostly prevented from entering, but small molecules such as synthetic chemicals can pass through relatively easily. Peptides have an intermediate ability to overcome these barriers because they are the same size as synthetic pesticides and protein biologics. The inherent bioavailability of peptides may be sufficient to directly attack internal receptors such as those in the nervous system. For example, the recently approved peptide GS-w/k-Hxtx-Hv1a targets the same receptors as two major classes of synthetic pesticides, and commercially available formulations can kill insects on contact.

Performance Optimization on Structure and Formulation

Improving the stability and bioavailability of natural peptides is an important goal in the discovery of new peptide-based drugs and pesticides. Optimization of the structure of natural peptides and proper formulation can result in more acceptable peptides or their mimetics, and optimization of delivery systems can also result in peptide products with better bioavailability.

Structural Optimization

To overcome the hurdles of low stability and weak activity of natural peptides, various structure optimization methods have been developed, including amino acid substitutions, cyclization strategies, mimetic designs, etc. (Yao *et al*., 2018; Muttenthaler *et al*., 2021). Natural peptides can be modified by genetic engineering to obtain new peptides with desirable properties. Such as, the bioinsecticide Spear® was developed using genetic engineering to add a glycine-serine dipeptide to the natural spider venom peptide ω/κ-HXTX-Hv1a. This product has higher activity, lower risk, and longer shelf life than natural products, so it is considered a sustainable and effective green pest control tool (GPCT) in agriculture and public health (Tan and Tong, 2022).

Formulation Development

The development of various formulations such as suspensions, microemulsions, and capsule suspensions can prevent the degradation of peptide molecules due to environmental factors such as water, UV light, temperature, and metabolic enzymes. This not only increases stability but also improves bioavailability as these formulations can easily enter the body through the epidermis and reach target sites (Tan and Tong 2022). Likewise, the rainproof amphiphilic peptide thanatin (THA) AMP dermaseptin 01 (DS01) is tightly anchored to the surface of soybean leaves when sprayed. A fusion of the antimicrobial peptide DS01 and THA (DS01-THA) inhibits the germination of *P. pachyrhizi* spores and alleviates Asian soybean rust in vitro (Schwinges *et al*., 2019). Moreover, peptide formulations mixed with chemical insecticides through various mechanisms can extend the spectrum of activity and delay resistance (Gonzalez *et al*., 2002; Lopez-Garcia *et al*., 2003). Hexapeptide PAFs can inhibit fungi (*Alternaria* sp.) that are not affected by commonly used fungicides (Lopez-Garcia *et al*., 2003). Hexapeptide 66-10 and heptapeptide derivatives 77-3 and 77-12 can act synergistically with thiabendazole (TBZ) to delay the resistance of *Fusarium sambucinum* to TBZ (Gonzalez *et al*., 2002).

Delivery Systems (DSs)

Drug delivery systems (DDSs) can deliver the appropriate amount of drug to the target through controlled release technologies such as hydrogels, cubosomes, and nanocarriers, increasing the efficiency of drug utilization (Nordstrom and Malmsten 2017; Martin- Serrano *et al*., 2019). Easily degraded peptides can be used in combination with new DDSs strategies for precision agriculture. Inject insecticidal peptides into plant lectins or viral coat proteins to improve utilization and insecticidal activity (Nakasu *et al*., 2014). Herzig *et al*. (2014) delivered insecticidal toxins released by transgenic insect pathogens such as baculovirus, the soil bacterium *Bacillus thuringiensis*, and the fungus *Metarhizium*. These pathogens can infect insects and simultaneously express insecticidal toxins, thereby achieving a synergistic insecticidal effect (Herzig *et al*., 2014).

Biosynthesis of Peptides (BSPs)

Peptides are generally prepared by chemical synthesis methods called "liquid phase synthesis" and "solid phase synthesis”. However, chemical synthesis is expensive and there are limits to large-scale production. Therefore, many studies are aimed at obtaining peptides more economically. Peptide biosynthesis using enzymes, fermentation, and genetic engineering methods is preferred due to its advantages, such as widely available raw materials and low cost (Akbarian *et al*., 2022). Heterologous systems currently used for peptide production include bacteria such as *Escherichia coli* and *A. subtilis* and fungi such as *Pichia pastoris* and *Saccharomyces cerevisiae*, plants (cell and tissue culture), and related strategies to achieve higher-performance peptide production (Parachin *et al*., 2012; Narayani *et al*., 2020). Cyclic peptides are obtained through biosynthesis in fungi, bacteria, and plants (Narayani *et al*., 2020). Therefore, the production of peptide pesticides by biosynthesis is worthy of further study. Advantages and disadvantages of using antimicrobial peptides to treat plant pathogens described in table 15.

Table 15. Advantages and Disadvantages of using Antimicrobial Peptides to Treat Plant Pathogens

Advantages	Disadvantages
AMPs rapidly kills both fungal and bacterial pathogens at all stages, including spores	The systemic effects of AMPs are weak and cannot eliminate pathogens within the host plant
AMP slowly selects resistant pathogens	Because AMP has a strong inoculating effect, the concentration used must be carefully determined.
AMPs can be easily incorporated into plants through transgenic transformation	Expression of AMPs in plants depletes resources used for growth and reduces yield
AMPs act synergistically with many other antimicrobial agents	Manufacturing AMPs remains relatively expensive
AMPs manipulate symbionts within plants and promote plant growth and development	Long-term exposure to AMPs can lead to the selection of resistant pathogens

Future Concerns

Create modern functional peptides utilizing target-oriented approaches to move forward selectivity against plant pathogens, optimize soundness within the plant environment, and provide low poisonous quality. Design and validate peptide details to extend the adequacy and shelf life of the peptides. Provide appropriate strategies for conveying the peptide definitions to the plant, particularly with endotherapy devices, to protect trees against endophytic bacterial plant pathogens. Establish a large-scale production processor that is more affordable, maintainable, and capable of fulfilling the demands of producers for plant protection. Conduct field experiments using the most relevant diseases and crops to evaluate and approve the effectiveness and application of plant-protection products made of functional peptides.

Conclusion

The past 120 years have seen the emergence of peptides and the rapid development of peptide-based drugs and pesticides development for human and agriculture development. Global trends are for products with high efficiency, low toxicity, and environmental safety. The field of peptide, pesticides are maturing in several aspects, including long-term and extensive research into the utilization, production, and discovery of numerous agricultural peptides as potential candidates in agriculture. Several promising technologies in structure optimization, formulation, delivery systems, and biosynthesis will continue to contribute to the growth of peptide base pesticides. Peptides that meet high efficiency and safety requirements are useful for crop protection in organic agriculture. The industrialization of peptides is quickened by quick advancements in molecular biology, organic chemistry, synthetic biology, and hereditary building. In addition to X-ray crystallography, AlphaFold2 and RoseTTAFold can now be used to obtain 3D structures of proteins, and other new methods (phage peptide libraries, mRNA display, virtual screening) can be used to identify useful peptides. The developed peptides have high target affinity, meaning that very small amounts of peptides are sufficient to control weeds, pathogens, and insects. Due to the lower dosage of fully or partially fermented peptides, the cost is more competitive than existing pesticides. Peptides can probably become the most important for crop protection. Tt is not possible in this manuscript to discuss all aspects of peptides as new tools for plant protection in organic agriculture. However, I would like to draw the attention of biochemists, molecular biologists, and agronomists to this new field and promote more detailed and thorough research of peptide-based pesticides for the sustainable development of green agriculture. Synthetic pesticides are too expensive, too slow to develop, and unsustainable for the environment. Biopesticides address these deficiencies. Biopesticides are faster to develop, cheaper, and environmentally sustainable. Peptides offer the safety profile of microbial biopesticides combined with the efficacy of synthetic pesticides. Taken together, these properties make peptides a sustainable alternative to synthetic pesticides. The biotech revolution in agriculture is getting closer and closer. In crop protection, there is a strong desire to move away from synthetic pesticides and toward more sustainable pesticides, but failure to maintain pesticide effectiveness can increase risks to food security. The dual properties of sustainability and efficacy make peptide-based biologics formulation an ideal candidate to replace synthetic drugs and form the backbone of a green future in crop protection.

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