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Peptides, new tools for plant protection in eco-agriculture

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ABSTRACT

As important physiological regulators, peptides have been used in many fields including medicine, cosmetics, healthcare products, animal nutrition and health, and plant nutrition and protection. In recent years, peptides have become a popular research subject in plant protection as antimicrobial and immune inducers, plant growth regulators, insecticides, and herbicides for their extensive raw material sources, excellent activity, and ideal environmental compatibility. This paper briefly introduces peptide research progress, presents an overview of peptide studies in plant protection, and summarizes the application of the peptides in plant protection and prospects for peptides as green agrochemicals.

1. Introduction

Pesticides, an important tool for plant protection, play a key role in agriculture and food security. Without the use of pesticides, there would be a 78% loss in fruit production, a 54% loss in vegetable production, and a 32% loss in cereal production.[1] Therefore, pesticides contribute to increasing crop yields worldwide but require updates to meet the demands of agricultural development and environmental safety requirements. In the era of ecological agriculture, which focuses on sustainable development, there is an urgent need for effective, eco-friendly pesticides that provide activity against pests while presenting a low risk to nontarget organisms.

In recent years, peptides emerged as a rising new star in the field of plant protection due to the wide availability of raw material,[2–4] excellent activity,[5] and ideal environmental compatibility.[6,7] They have been applied as antimicrobials and immune inducers, plant growth regulators, insecticides, and herbicides to protect plants from bacteria, virus, pests, and weeds. To date, 18 peptides have been commercialized as green agents for plant protection. The bioinsecticide Spear®, derived from a neuropeptide of spider venom (the Blue Mountains funnel-web spider), won the Presidential Green Chemistry Challenge Award (Small Business Award) in 2020 and the Best New Biological Agent Award in 2021 in the USA. Peptides with excellent quality and success stories like Spear® are regarded as an important new tool for plant protection, making them very attractive in the research and development of green agrochemicals.

Discovery of new peptide pesticides requires an understanding of the research and application of existing peptides. This paper briefly introduces peptide research progress, presents an overview of peptides in plant protection, and summarizes the application of peptides in plant protection and future prospects of green agrochemicals.

2. Progress in peptide research

2.1. General introduction on peptides

Peptides are short-chain biomolecules of between two and fifty amino acids, linked by peptide bonds. They are also obtained from the intermediate products of protein hydrolysis. According to their composition, peptides can be classified as homomeric or heteromeric, the former being completely composed of amino acids while the latter contain amino acids and nonamino acids, such as glycopeptides. All but cyclic peptides have an *N*-terminal (amine group) and *C*-terminal (carboxyl group) residue. Based on their sources, peptides are also categorized as natural and artificially synthesis peptides. Most natural peptides are from animals, plants, and microorganisms. Natural and synthetic peptides both can be produced through chemical synthesis, biological fermentation, gene recombination and other methods. Peptides are ubiquitous in living organisms and modulate many physiological processes, making them a common research subject in medicine, cosmetics, and agriculture etc.

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Abbreviations

SPPS	solid phase peptide synthesis
EGF	epidermal growth factor
AMPs	antimicrobial peptides
APD3	antimicrobial peptide database
MRL	Maximum Residues Limit
PHC	Plant Health Care
PGRPs	plant growth-regulating peptides
ABA	abscisic acid
DA	Destruxin A
IKs	insect kinins
PBAN	pheromone biosynthesis activating neuropeptide
ASTs	allatostatins
PA1b	Pea Albumin 1 subunit b
THA	thanatin
DS01	dermaseptin 01
DS01-THA	DS01 and THA
DDS	drug delivery systems
TBZ	thiabendazole

2.2. Overview of peptide research

Secretin was the first peptide to be identified, found in 1902 by Bayliss and Starling in the gastrointestinal tract of animals.[8] Later functional peptide discoveries included insulin, which reduces blood glucose, and oxytocin, which promotes uterine contraction. The invention of solid phase peptide synthesis (SPPS) in 1963 laid the foundation for automatic synthesis, because SPPS took less time and was a simpler process than traditional liquid phase synthesis. For this advance, Merrifield, the inventor of SPPS, won the Nobel Prize in Chemistry in 1984. Since then, peptide studies entered a phase of rapid development. 10 Nobel Prizes have been awarded for peptide-related work, speaking to their extraordinary significance in science and technology. For instance, epidermal growth factor (EGF), a small 53-amino-acid peptide, promotes cell growth in the skin and cornea, and its discoverer was awarded the Nobel Prize in Physiology or Medicine in 1986. Signal peptides control cellular transport and localization and help to make more effective use of cells as "protein factories" to produce drugs. Their discovery was awarded a Nobel Prize in Physiology or Medicine in 1999. Peptides produced by phages can be used to fight autoimmune diseases, and their discovery was awarded a Nobel Prize in Chemistry in 2018. Particularly, a neuropeptide-based bioinsecticide Spear® won the Presidential Green Chemistry Challenge Award in 2020, which draw people's attention to peptide application in the field of plant protection. Key milestones in the history of peptide development are shown in Fig. 1.

Research on peptides focuses on peptide sources, structures, structural optimization, production, function, and applications (Fig. 2). As important physiological regulators with multiple functions, peptides are widely used in medicine, cosmetics, animal nutrition and healthcare, and plant growth and protection. More than 80 peptide drugs have been marketed for diabetes, cancer, osteoporosis, multiple sclerosis, HIV infection, and chronic pain.[9] More than 50 peptide drugs are in clinical development and 400–600 peptide drugs are in preclinical studies.[9] Given their extensive application in medicine, many scientists have begun to explore their possible application in plant protection in modern agriculture.

3. Overview of peptide research in plant protection

3.1. Research trends

We performed a search of peptide-related publications in the Web of Science and SciFinder databases (Fig. 3) in 10-year blocks from 1902 to 2022 by using "peptide" as the main search term and "insecticide," "fungicide," "herbicide," and "plant growth regulator" as sub-terms. There were few publications during the first 60 years after the discovery of secretin in 1902, as peptides were not yet the subject of research in plant protection (Fig. 1). Since 1962, when the book Silent Spring was published by Rachel Carson, people began to pay attention to protecting the environment as well as protecting plants from pests using environmentally friendly agrochemicals. Environmentally safe peptides then became an attractive subject for agricultural applications. Coincidentally, the rapid and efficient SPSS method was invented in 1963, enabling automatic peptide synthesis and ensuring plentiful supply. Since then,

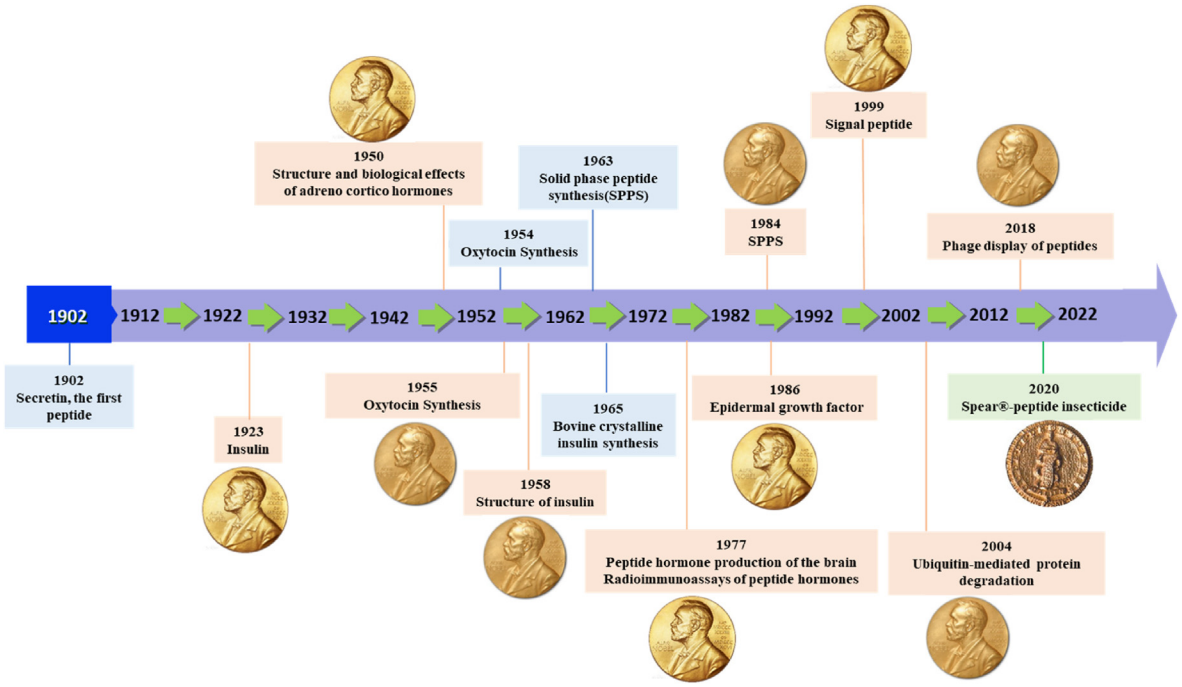

Fig. 1. Timeline of significant milestones in the history of peptides.

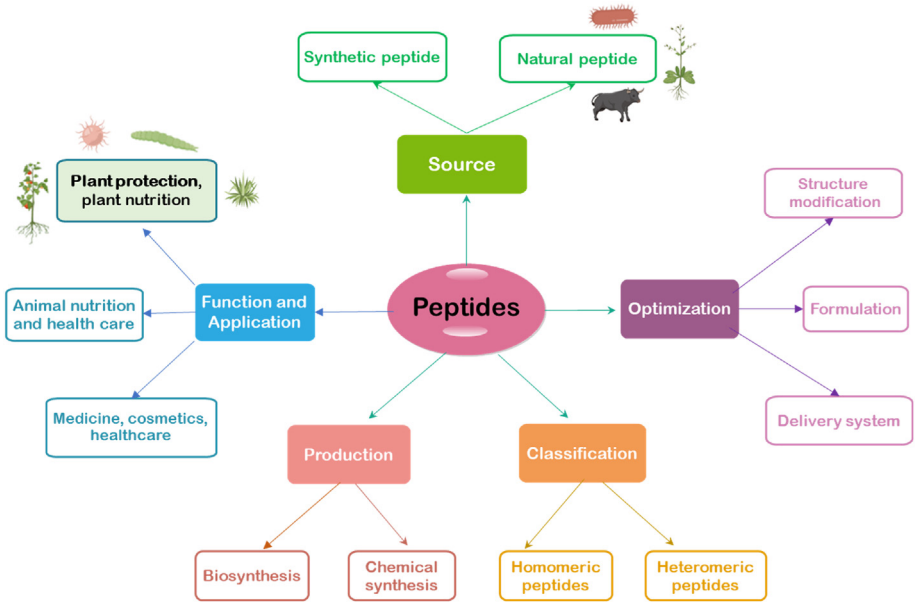

Fig. 2. Outline of peptide research on sources, classification, optimization, production, application.

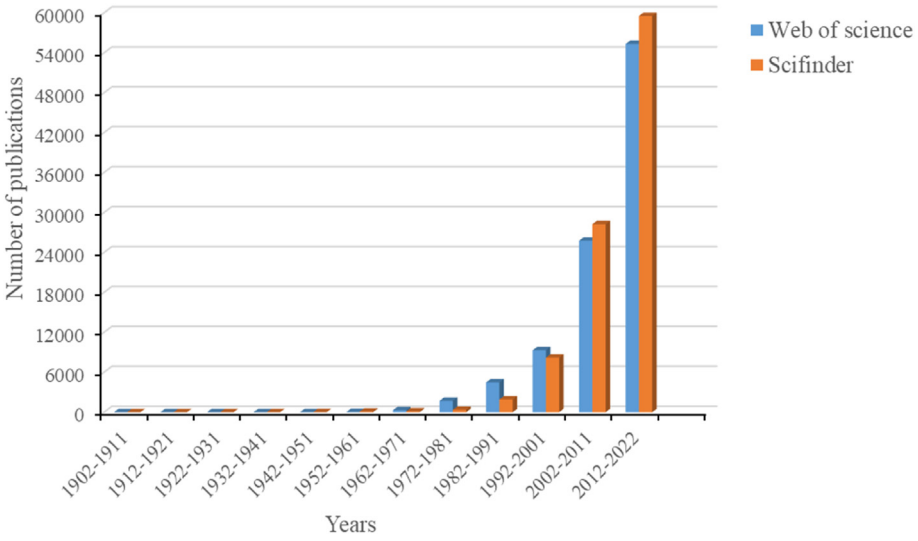

Fig. 3. Distribution of peptide publications in plant protection from 1902 to 2022.

peptide research in plant protection began to increase from 1972 to 1991. In the last 30 years, the frequency of publication increased remarkably (1992–2022). In the Web of Science database, the number of relevant citations from 1992 to 2022 was 90,395, accounting for 93.0% of the 96,936 publications (1902–2022). Similarly, the SciFinder database yielded 98,381 publications in the past three decades, comprising 99.9% of the 98,496 publications (1902–2022). The retrival results from the two databases both indicate that the peptide-related work in plant protection has drawn increasing attention in recent years.

3.2. Cooperation between nations and institutions in peptide research

Countries represented in the field of peptide research in the context of plant protection (Fig. 4, data from the Web of Science database) show the United States is the leader in the field with not only the largest number of publications (25,328, 26.13%) but also the most extensive foreign cooperation, followed by China (16,125, 16.63%). The institution with the largest number of publications was the University of California System (3,005, 3.10%), followed by Udice French Research Universities (1,957, 2.02%), and Centre National de la Recherche Scientific (1,940, 2.00%) (Fig. 5, data from Web of Science). Meanwhile, the United States and China are the top two countries with the largest number of publications in the SciFinder database. The top three institutions with the largest number of publications are the University of California System (1,463, 1.49%), China Agricultural University (1,287, 1.31%), and the Chinese Academy of Sciences (897, 0.91%).

4. Application of peptides in plant protection

Peptides have advantages in efficient and eco-friendly strategies for pest management in green agriculture. They have been used as antimicrobial agents and plant immune inducers, plant growth regulators, insecticides, and herbicides.

4.1. Antimicrobial and immune-inducing peptides

Plant pathogens attack crops and lead to serious adverse impacts on their growth. Traditional chemical fungicides are effective in preventing

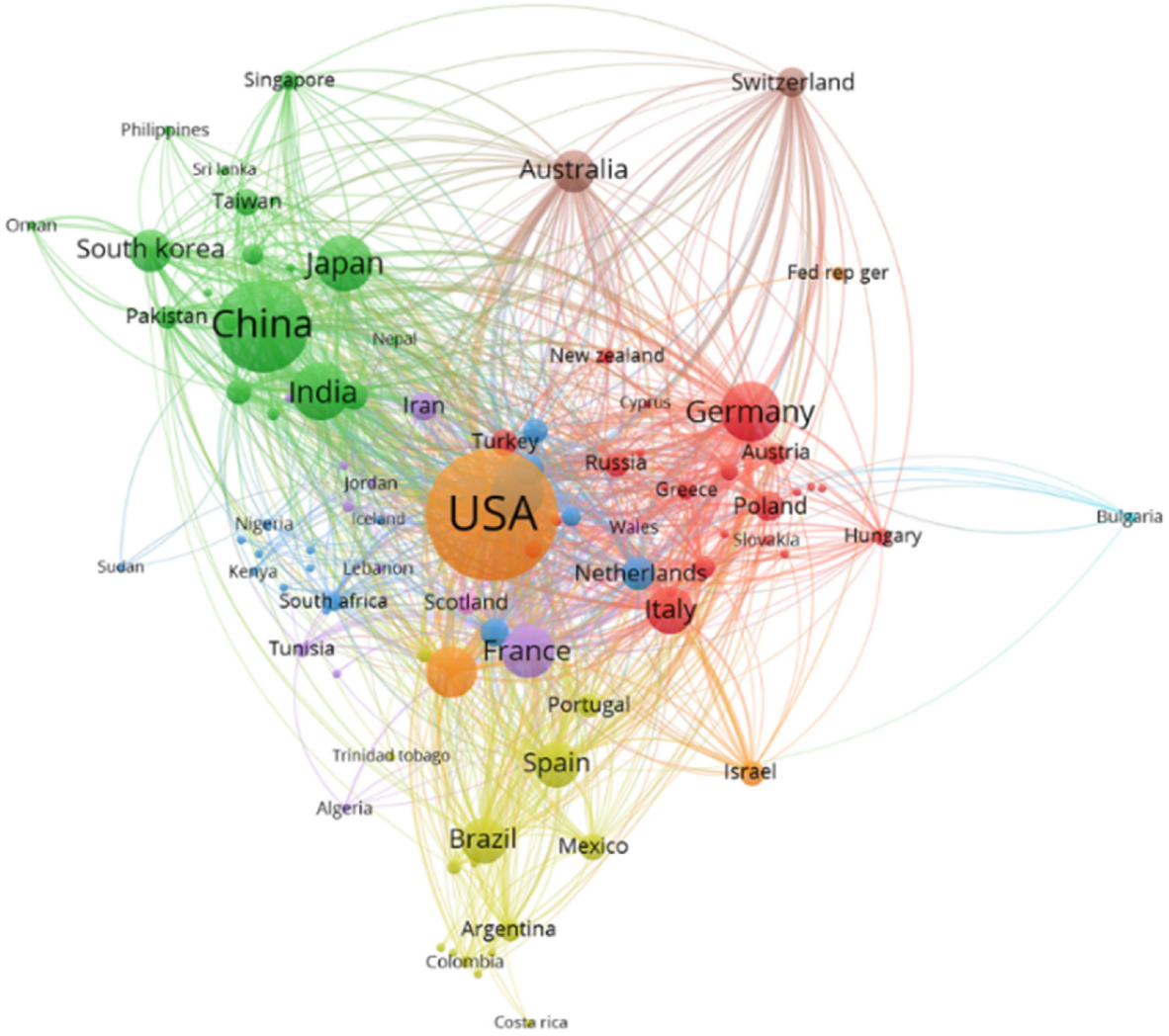

Fig. 4. Worldwide collaborations among countries in the field of peptides in plant protection (Web of Science database).

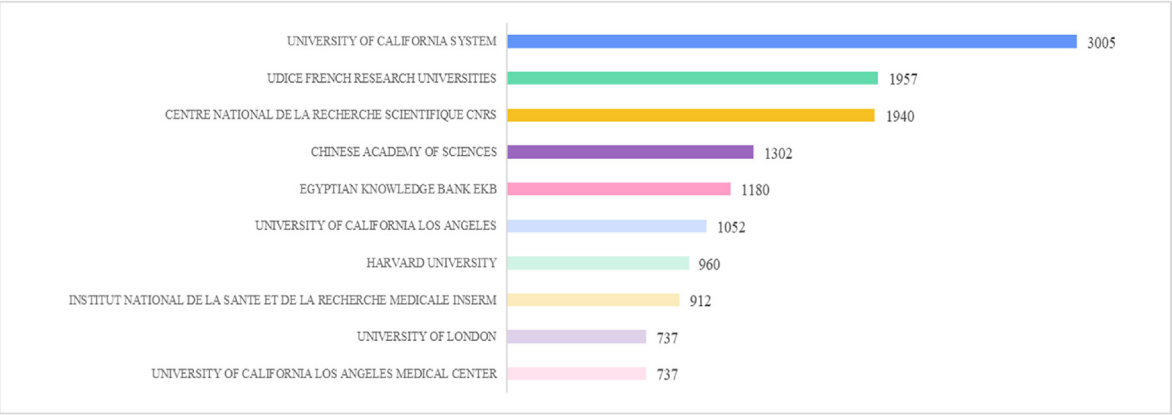

Fig. 5. Top 10 institutions with the largest number of publications in the field of peptides in plant protection from 1902 to 2022(Web of Science database).

diseases caused by plant pathogens; however, their long-term continuous use has led to resistance and their residues present a risk of harm to humans and the environment. More sustainable methods to control plant diseases are urgently needed.[10] Naturally occurring antimicrobial peptides (AMPs) mediate the innate host defense and can be used as immune inducers. Given their high specificity, rapid degradation, and efficacy, AMPs are expected to be a promising first line of defense against fungi, viruses, and bacteria.[11,12]

4.1.1. AMPs

A total of 3425 AMPs have been reported in the antimicrobial peptide database (APD3) (*http://aps.unmc.edu/AP/*, accessed June 30, 2022).

Selections of AMPs with agricultural activity are listed in Table 1. Artificial peptides account for 49.33% of all listed peptides, followed by AMPs from plants (29.33%), animals (16.00%), and microorganisms (5.33%) (Fig. 6A). Natural AMPs are generated from animals, plants, and microorganisms.[13,14] Cathelicidins and defensins represent the two major AMP families in mammals.[15] PGQ and Magainin II are produced by frogs, which are the main source of AMPs in amphibians.[16] AMPs from insects include defensins, cecropins, drosocins, attacins, diptericins, ponericins, metchnikowins, and melittin.[17] AMPs in fish were reviewed elsewhere.[18] Plant AMPs are generally classified based on their sequences and structures as thionins, defensins, hevein-like peptides, knottins, stable-like peptides, lipid transfer proteins, snakins, and cyclotides.[13] Bacteria and fungi are also repositories of AMPs.[19] AMPs from bacteria are not generated to prevent infection, but as a competitive strategy to kill other microorganisms competing for nutrition in the same ecological niche and ensure the survival of a single bacterial cell.[20] Synthetic peptides can be synthesized by chemical methods and screened from combined libraries (bacterial two-hybrid system screening peptide library,[21] yeast-based two-hybrid library,[22] phage display[23]) based on their affinity and specificity for important target proteins.

AMPs have a wide range of inhibitory effects against bacteria, fungi, parasites, and viruses. For example, animal PVEC acts against *Bacillus megaterium* and plant PhD2 acts against *B. cinerea*. Microbial NAF has antimicrobial activity against *Aspergillus flavus*, *Fusarium solani*, and *Penicillium italicum*. Synthetic Alf-AFP is effective against *Verticillium dahlia*. Several AMPs under development are listed in Table 1. BLAD, a peptide produced during germination of *Lupinus albus,*[24] has been developed into two products, ProBlad® Verde from the American company Sym-Agro and Problad Plus™ from the Portuguese company Consume em Verde.

Problad Plus™ (https://www.cev.com.pt/) is a biofungicide containing 20% BLAD that acts on susceptible fungal pathogens by causing damage to cell walls and inner membranes. It is effective against pathogens such as powdery mildew and gray mold, and is recommended for crops such as strawberries, grapes, tomatoes, and drupes (peaches, cherries, etc.). Problad Plus™ is also suitable for rotation with chemical fungicides to reduce harmful residues and reduce the likelihood of resistance. ProBlad® Verde (https://sym-agro.com/problad/), controls fungal and bacterial diseases in an unprecedented multisite mode of action. It is now registered for crops such as vine berries, herbs, coffee, leafy greens, and mustard plants to combat coffee leaf rust, white mold, gray mold, powdery mildew, anthracnose, bluegrass leaf rust, leaf blight, and rhizopus. The product achieves reliable disease control with a late-onset activity up to 7 days and a disease prevention period up to 14 days. The product has been granted an exemption from the European Union's Maximum Residues Limit (MRL) to help growers of high-value export crops meet increasingly stringent standards.

4.1.2. Immune inducing peptides

Their functions in innate host defense mean AMPs can act as immune inducers, trigger defense signals, or enhance innate immunity in plants.[25,26] Three varieties of peptide have been explored as commercial immune inducers.

Peptide maSAMP (https://www.invaio.com/), from Invaio Sciences, is used to control citrus Huanglongbing, a destructive disease. The peptide kills *Liberobacter asianticum Jagoueix*, the bacteria that cause Huanglongbing disease, and activates the plant's immune system to prevent subsequent infection. The spiral structure of maSAMP quickly penetrates the bacterial membrane, causing it to lyse within half an hour. Given the lack of effective products to control this disease, maSAMP is expected to be a powerful tool.

PREtec technology (https://www.planthealthcare.com/), from the American Plant Health Care (PHC) company, was patented in the United States in 2019. Its unique immune-inducing peptides and its mixtures with other products have been recognized for strengthening plant resistance to disease and stress, as well as promoting plant growth. All PREtec peptides are variants of natural proteins and break down rapidly in the environment, leaving no harmful residues on the crop or in the environment. In 2021, PHC launched PHC279 with PREtec technology in Brazil and sold it under the name of Saori™. This product is used as a seed treatment to prevent Asian soybean rust.

FLG22 (https://phytotechlab.com/), from Phytotech, induces the natural immune response. Its sequence was derived from the highly conserved *N*-terminal region of *Pseudomonas aeruginosa* flagellin. FLG22 and its derivatives induce defense responses in *Lycopersicon esculentum* and *Arabidopsis thaliana* and have elicitor activity.

Many immune induction peptides are in development. PIP1 and PIP2 enhance the immune responses and pathogen resistance in Arabidopsis.[27] *Nicotiana tabacum* NbPPI1 stimulates the immune response and enhances plant resistance to *Pytophthora*.[28] Maize immune signal peptide Zip1 reduces the virulence of maize smut fungus.[29] Inceptin is involved in herbivorous defense of cowpea and kidney bean by triggering an increase in defense-related plant hormones salicylic acid and jasmonic acid.[30,31] Treating plants with Inceptin produces volatile organic molecules, such as indole and methyl salicylate, that attract the natural enemies of *Spodoptera frugiperda*, and thus mediate indirect defense. Thirty new putative CAPE1-like peptides, identified in Vitinaceae, Solanaceae, Fabaceae, Brassicaceae, and *N. tabacum*, are involved in defense responses of various plants.[32] Pep-13 from *Phytophthora sojae* triggers an immunoreaction in parsley.[33]

4.2. Plant growth-regulating peptides

Plant growth and development is influenced by plant hormones, including auxin, cytokinin, and gibberellin, which mediate intercellular communication during development. However, recent studies have shown that peptide signal molecules also play important roles in diverse development processes in plants as well as environmental responses,[34–39] such as differentiation of meristematic stem cells, formation of tissues and individual organs, fruit maturation, abscission,[40]and adaptation to biotic and abiotic stress.[41,42] Plant growth-regulating peptides (PGRPs) are a new class of plant hormones[37] with signal properties and hormone characteristics,[40] and they have remarkable biological activities at very low concentrations (10^{-7}–10^{-9} M). These findings indicate the importance of peptides in regulating plant growth.

About 30 peptide phytohormone families have been identified in plants and many more exist in various plant-interacting organisms, such as bacterial and fungal pathogens, plant-parasitic nematodes, as well as symbiotic and plant-beneficial bacteria and fungi.[43] To date, seven classes of peptide phytohormones (CLE, CEP, RALF, IDA, PSK, PSY, and PEP) have been found in plant-interacting bacteria, fungi, and nematodes.[43] The precursors of these peptides are processed into mature peptides in plants, and then interact with plant receptors and activate downstream signal pathways, leading to growth responses. Some peptides and their functions as plant growth regulators are summarized in Table 2. The sources of these PGRPs are described in Fig. 6B, which shows that plant peptides account for 58.93%, followed by synthetics 19.64%, microorganisms 14.29%, and animals 7.14%.

PGRPs have extensive functions in plant growth and development. For example, the functional peptide PY91 found by TIBO Crop Science in 2021 interferes with crop growth. The CLAVATA3 peptide regulates meristem size.[44] SCR peptide is a recognition factor for self-incompatibility of cruciferous pollen.[45] RALFs are a family of peptides that function in plant cell growth.[46] The root-derived CLE25 peptide enables plants to cope with drought stress by modulating the expression of NCED3,[47] which increases abscisic acid (ABA) levels[48–50] to induce stomatal closure and maintain water balance. Peptide hormones can also enhance or inhibit the effects of traditional plant hormones. For example, CLE41/TDIF, BR peptides, and auxin jointly regulate root formation. In contrast, the expression of CLE27 is inhibited by auxin.

Four types of peptides have been used as commercial plant growth regulators. Italy Hello Nature has developed the KEYLAN series of natural

Table 1
Classification and agricultural bioactivity of some antimicrobial peptides.

AMPs from Animals				
Peptide	Source	Function	Species effectiveness	Refs.
Abaecin	*Apis mellifera*	Antibacterial	*Agrobacterium tumefaciens* *Erwinia salicis* *Pseudomonas syringae* *Xanthomonas campestris*	[121]
Apidaecins	*Apis melifera*	Antibacterial	*A. tumefaciens* *E. salicis* *P. syringae* *Rhizobium meliloti*	[122,123]
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*	[124]
Dermaseptin	*Rhacophorus*	Antibacterial	*Xylella fastidiosa*	[125]
Drosomycin	*Drosophila melanogaster*	Antifungal	*Botrytis cinerea* *Fusarium culmorum* *Fusarium oxysporum* *Nectria haematococca* *Alternaria brassicola* *Alternaria longipes* *Trichoderma viride* *Ascochyta pisi*	[74]
Indolicidin	*Bovine*	Antibacterial	*X. fastidiosa*	[125]
LfcinB	*Bovine*	Antifungal	*P. digitatum* *Penicillium italicum* *Penicillium expansum* *Penicillium* sp. *Alternaria* sp. *Aspergillus nidulans* *B. cinerea* *F. oxysporum*	[126]
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*	[124]
Penetratin	*Drosophilid*	Antibacterial	*Bacillus megaterium*	[127]
PGQ	*X. laevis*	Antibacterial	*X. fastidiosa*	[125]
pVEC	Mammalian	Antibacterial	*B. megaterium*	[127]
Spodopsin Ia	*Spodoptera litura*	Antibacterial	*B. megaterium*	[128]
AMPs from Plants				
α1-purothionin	*Triticum aestivum*	Antibacterial	*Xanthomonas* *Erwinia*	[129]
BLAD	*Lupinus albus*	Antifungal	*B. cinerea* Erysiphales	[24]
Ca-AFP	*Capsicum annuum*	Antifungal	*F. oxysporum* *Phytophthora capsici*	[130]
Ca-LTP1	*C. annuum L.*	Antifungal	*F. oxysporum* *Colletotrichum lindemuthianum*	[131]
J1	*C. annuum*	Antifungal	*Colletotrichum gloeosporioide* *Colletotrichum musae* *F. oxysporum*	[132,133]
maSAMP	*Citrus australasica F.Muell*	Antibacterial	*Liberobacter asianticum Jagoueix*	[134]
NaD1	*Nicotiana alata*	Antibacterial, Antifungal	*B. cinerea* *F. oxysporum* *F. oxysporum f. Sp. Vasinfectum* *Thielaviopsis basicola* *Verticillium dahlia* *Leptosphaeria maculans* *A. nidulans* *Fusarium graminearum*	[135–137]
Pa-AFP1	*Passiflora alata Curtis*	Antifungal	*C. gloeosporioide*	[138]
Pe-AFP1	*Passiflora edulis*	Antifungal	*Aspergillus fumigatus* *F. oxysporum*	[139]
Peptide-1	*Oryza sativa*	Antifungal	*Magnaporthe oryzae*	[140]

(*continued on next page*)

Table 1 (*continued*)

Pf2	*Passiflora edulis f. Flavicarpa*	Antifungal	*F. oxysporum* *C. musae* *C. lindemuthianum*	141
PhD1	*Petunia hybrida*	Antifungal	*B. cinerea* *F. oxysporum*	20,142
PhD2	*P. hybrida*	Antifungal	*B. cinerea*	20,142
PvD1	*Phaseolus vulgaris*	Antifungal	*F. oxysporum* *Fusarium solani* *Fusarium laterithium*	143
SD2	*Helianthus annuus*	Antifungal	*Sclerotinia sclerotiorum*	144
Snakin-1	*Solanum tuberosum*	Antibacterial, Antifungal	*B. cinerea* *F. solani* *F. culmorum* *F. oxysporum* *Plectosphaerella cucumerina* *Colletotrichum lagenarium* *Colletotrichum graminicola* *Bipolaris maydis* *Aspergillus flavus* *C. michiganensis* *Ralstonia solanacearum*	145,146
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*	145
Snakin-Z	*Ziziphus jujuba*	Antifungal	*Pythium ultimum* *Aspergillus niger*	147
Thi2.1	*Arabidopsis thaliana*	Antifungal	*F. oxysporum*	148
Tn-AFP1	Coconut water *Trapa natans*	Antifungal	*F. oxysporum* *Mycosphaerella arachidicola*	149
ZmD32	*Zea mays*	Antibacterial, Antifungal	*F. graminearum*	135
ZmPep1	*Z. mays*	Antifungal	*Helminthosporium* *Pythiumspp .* *Fusarium*	150
AMPs from microorganism				
AFP	*Aspergillus giganteus*	Antifungal	*F. culmorum* *Fusarium equiseti* *Fusarium lini* *Fusarium moniliforme* *F. oxysporum* *Fusarium poae* *Fusarium proliferatum* *F. solani* *Fusarium sporotrichoides* *Fusarium vasinfectum* *Magnaporthe grisea* *P. infestans*	151
ANAFP	*A. niger*	Antifungal	*A. fumigatus* *A. flavus* *F. oxysporum* *F. solani*	151
NAF	*Penicillium nalgiovense*	Antifungal	*A. flavus* *F. solani* *P. italicum*	151
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*	151–153
Others				
α_P2	Synthesized	Antifungal	*P.capsici*	23
Alf- AFP	Recombinant expression	Antifungal	*Verticillium dahliae*	80
CAMEL	Rational-designed	Antibacterial	*Pectobacterium carotovorum*	154

(*continued on next page*)

Table 1 (*continued*)

Cecropin P1	Recombinant expression	Antibacterial	*Pectobacterium chrysanthemi* *P. syringae* *Pseudomonas marginata* *E. carotovora*	155
CEMA	Rational-designed	Antifungal	*F. solani*	156
Dm-AMP1	Recombinant expression	Antifungal	*B. cinerea*	157
DS01-THA	Rational-designed	Antifungal	*Verticillium alboatrum* *Phakopsora pachyrhizi*	112,158
D4E1	Rational-designed	Antibacterial, Antifungal	*Colletotrichum destructivum* *A. tumefaciens* *Xanthomonas populi*	159–161
D32R	Rational-designed	Antibacterial, Antifungal	*F. oxysporum* *P. cucumerina* *B. cinerea* *X. campestris pv. Translucens* *C. michiganensis*	162
ESF12	Rational-designed	Antifungal	*Septoria musiva*	163
Iseganan	Rational-designed	Antibacterial	*P. carotovorum* *P. chrysanthemi*	154
KYE28	Rational-designed	Antibacterial	*Xanthomonas vesicatoria* *Xanthomonas oryzae*	164
MB39	Rational-designed	Antibacterial	*P. syringae* *Erwinia amylovora*	165,166
Mj- AMP1	Recombinant expression	Antifungal	*Alternaria solani*	167
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*	124,168,169
MSrA1	Rational-designed	Antibacterial, Antifungal	*E. carotovora* *Phytophthora cactorum* *F. solani*	170
MsrA2	Rational-designed	Antibacterial, Antifungal	*E. carotovora* *Pythium irregulare* *Pythium paroecandrum* *F. solani* *Rhizoctonia* *Phytophthora* *Pythium* sp. *F.oxysporum* *Alternaria alternata* *B. cinerea* *P. carotovorum*	171,172
MsrA3	Rational-designed	Antibacterial, Antifungal	*E. carotovora* *P. infestans* *Phytophthora erythroseptica*	173
Myp30	Rational-designed	Antibacterial, Antifungal	*E. carotovora* *Peronospora tabacina*	174
NCR044	*Medicago truncatula*	Antifungal	*B. cinerea* *Fusarium* spp.	175
NoPv1	Peptide aptamer library	Antifungal	*P.viticola* *P.infestans*	22
O3TR, C12O3TR	Rational-designed	Antifungal	*P. digitatum*	176
Peptaibol	Chemically modified	Antifungal	*B. cinerea* *Bipolaris sorokiniana* *F. graminearum* *P. expansum*	177
Pep11	Rational-designed	Antifungal	*P. infestans*	178
Pexiganan	Rational-designed	Antibacterial	*P. carotovorum* *P. chrysanthemi*	154
PV5	Rational-designed	Antibacterial, Antifungal, Antiviral	*E. carotovora* *fungi* *TMV*	179
Γ NFAP-opt, Γ NFAP-optGZ	Rationally designed	Antifungal	*C.herbarum*	180
SB-37	Rational-designed	Antibacterial	*E. carotovora*	181
Shiva-1	Rational-designed	Antibacterial	*Pseudomonas solanacearum* *E. carotovora* *Phytoplasma*	182–184
SNP-D4	Peptide aptamer library	Antifungal	*M.oryzae*	21

(*continued on next page*)

Table 1 (*continued*)

Tachyplesin I	Recombinant expression	Antibacterial, Antifungal	*V. dahliae* *E. carotovora*	185
TK VI	*Trichoderma pseudokoningii strain SMF2*	Antifungal	*B. cinerea* *F. oxysporum* *Ascochyta citrulline* *Phytophthora parasitica*	186,187
VG16KRKP	Rational-designed	Antibacterial	*V. dahliae* *X. oryzae* *X. campestris*	188
10 R,11 R	Rational-designed	Antibacterial, Antifungal, Antiviral	*E. carotovora* Fungi TMV	189

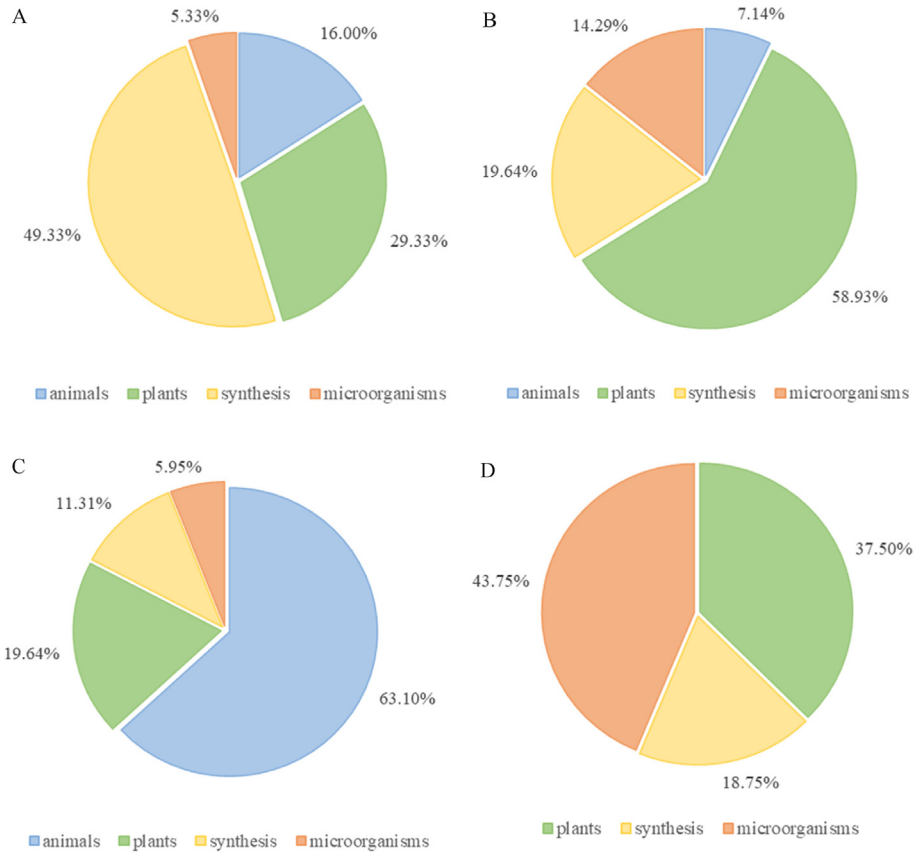

Fig. 6. The source situation of peptides with antimicrobial (A), plant growth regulator (B), insecticidal (C) and herbicidal (D) activities for plant protection.

products (https://www.hello-nature.com/us/), including KEYLAN Ca, KEYLAN Combi, KEYLAN Fe, KEYLAN Max, KEYLAN Mn, and KEYLAN Zn. These products provide micronutrients in a biochelated form and act as biostimulants. KEYLANs are used to prevent and treat malnutrition by fertilization of the soil or hydroponic cultivation. These products have excellent stability and water solubility, can be used over a broad range of soil pH, and can be paired safely with insecticides, fungicides, growth regulators, adjuvants, biocontrol protects, and other calcium foliar fertilizers.

The plant-derived peptide LRPP (https://www.hello-nature.com/us/) is also a biostimulant as the active ingredient of commercial product Tandem developed by Italy Hello Nature. It is a powerful biostimulant that improves resistance to environmental stresses, such as drought, low and high temperature, or poor soil. This product is used at the sowing stage to build a closer and mutually beneficial relationship with seeds.

Ea peptide 91,938 is an active ingredient of PHC-91398 developed by PHC (https://www.planthealthcare.com/). As a growth regulator, it provides protection against fungal and bacterial pathogens and nematodes by stimulating growth, natural plant defenses, and metabolism. Proposed uses include seed treatment or foliar spraying.

Hicure® (https://www.syngenta.com/en), which contains easily absorbed peptides and amino acids, is a natural biostimulant with excellent efficacy and flexibility, and has been proven to improve plant quality and enhance resistance to environmental stress. This product is applied as a conventional spray or maceration solution to achieve the best results before key development stages, changing pots and transplanting, environmental stress, or before transportation. Hicure® does not require professional equipment and is compatible with most plant protection and fertilizer products.

4.3. Insecticidal peptides

Control of insect pests is a major concern for agriculture, because pests can cause crop losses of 13%–16%.[51] Insect pests are predominantly controlled by chemical insecticides. Unfortunately, the widespread use of these products has led to pest resistance as well as harm to human health and the environment.[52] Thus, it is necessary to develop bioinsecticides as

Table 2
Some peptides and their functions as plant growth regulators.

Peptide	Source	Function	Refs.
PGR peptide from Animals			
CLE	*Heterodera* spp.	Activate downstream signaling pathway leading to growth response	43
	Globodera spp.		
	Rotylenchulus spp.		
	Meloidogyne spp.*16D10*		
	Meloidogyne spp.*MAP*		
CEP	*Rotylenchulus* spp.	Activate downstream signaling pathway leading to growth response	43
	Meloidogyne spp.		
Hicure®	Animal protein hydrolysates	Improve plant quality and enhance resistance to environmental stresses	190
IDA	*Meloidogyne* spp.	Activate downstream signaling pathway leading to growth response	43
PGR peptide from Plants			
AtRALF1	*A. thaliana*	Overexpression causes semi-dwarfism, exogenous peptide Causes cytoplasmic Ca^{++} spike and inhibition of hypocotyl elongation	87,191,192
AtRALF23	*A. thaliana*	Overexpression impairs brassinolide-induced hypocotyl elongation and causes semi-dwarfism	193
CEPs	*A. thaliana*	*N*-demand signaling, lateral root growth, nodulation	194,195
CIFs	*A. thaliana*	Casparian strip formation	78,196
CLE19	*A. thaliana*	Root apical meristem size	197
CLE25	*A. thaliana*	Improvement of ABA level	47
CLE41/44 (TDIF)	*A. thaliana*	Inhibition of xylem differentiation	76,98
CLE40	*A. thaliana*	Cell differentiation	198,199
CLV3, CLE2	*A. thaliana*	Stem cell renewal and differentiation	200–205
EPF2	*A. thaliana*	Stomata development	206
GmCLE40	*A. thaliana*	Stem cell differentiation	197
GRI	*A. thaliana*	Cell death control	207
IDA	*A. thaliana*	Floral organ abscission	208–210
LRPP	plants	Improve the resistance to environmental stresses	Hello Nature (*https://www.hello-nature.com/us/*)
MtCLE12	*A. thaliana*	Regulation of nodulation	211
MtRALFL1	*Medicago trunculata*	Overexpression causes reduced number and abnormal nodule development, regulated by bacterial nod factors	212
NaRALF	*Nicotiana attenuata*	RNAi downregulation causes long roots, abnormal root hairs	213
Phytosulfokine (PSK)	*A. thaliana*	Root and hypocotyl cell elongation	214–216
PSY	*A. thaliana*	Cell proliferation and expansion	77,217
PtdRALF1, PtdRALF2	*Hybrid Populus*	Exogenous peptide causes alkalinisation of cell culture growth medium	86
RALF1	*A. thaliana*	Extracellular alkalinisation	88
RALF23	*A. thaliana*	Extracellular alkalinisation	218
RGFs	*A. thaliana*	Root meristem activity, gravitropsism	97,219,220
SacRALF1	*Saccharum* spp	Exogenous peptide causes inhibition of microcalli development	192
SlPRALF	*Solanum lycopersicum*	Exogenous peptide causes inhibition of pollen tube growth	221
SlRALF	*Solanum lycopersicum*	Exogenous peptide causes alkalinisation of growth medium and inhibition of tomato and Arabidopsis root growth	222
Systemin	*A. thaliana*	Wound response	223
TobHypSys, TomHypSys	*A. thaliana*	Defence signaling	197
Tomato CLV3	*A. thaliana*	Stem cell renewal	224
PGR peptide from microorganisms			
CLE	*Actinobacteria* sp.	Mimic peptide phytohormones	43
	Thiotrichales sp.		
	Acidimicrobiaceae sp.		
	Gemmatimonadetes sp.		
	Actinobacteria sp. *Rhizophagus irregularis*		
	Rhizophagus diaphanous		
	Rhizophagus cerebriforme		
	Rhizophagus clarus		
CEP	*Ralstonia syzygii*	Mimic peptide phytohormones	43
Ea peptide 91,938	*E. amylovora*	Stimulate crop growth and enhance defense ability and stress resistance	PLANT HEALTH CARE (*https://www.planthealthcare.com/*)
IDA	*Melampsora larici-populina*	Mimic peptide phytohormones	43
	Colletotrichum fructicola		
PEP	*Metschnikowia* sp.*JCM33374*	Mimic peptide phytohormones	43
	Mycolicibacterium conceptionense		

(*continued on next page*)

Table 2 (*continued*)

PSK	*Tilletia* sp. *Colletotrichum* sp. *Lasiodiplodia* sp. *Diplodia* sp. *Macrophomina phaseolina* *Cercospora* sp. *Ramularia collo-cygni* *Pseudocercospora* sp. *Zymoseptoria* sp. *Proteobacteria* sp.	Mimic peptide phytohormones	[43]
PSY	*X. oryzae pv.oryzaeother* *Xanthomonas species*	Mimic peptide phytohormones	[43]
RALF	*F. oxysporum* other 26 fungi species *Streptomyces acidiscabies* other 8 species of Actinobacteria	Extracellular alkalinisation	[43]
Others			
CAMEL	Rational-designed	Inhibiting the growth of different species of Pectobacterium	[154]
CEP1	Rational-designed	Increases nutrient uptake rates along plant roots	[225]
KEYLAN Ca	Rational-designed	Optimizing Calcium uptake and boosting plant metabolism	Hello Nature (*https://www.hello-nature.com/us/*)
KEYLAN Combi	Rational-designed	Optimizing nutrient uptake and boosting plant metabolism	Hello Nature (*https://www.hello-nature.com/us/*)
KEYLAN Fe	Rational-designed	Optimizing Iron uptake and boosting plant metabolism	Hello Nature (*https://www.hello-nature.com/us/*)
KEYLAN Max	Rational-designed	Optimizing nutrient uptake and boosting plant metabolism	Hello Nature (*https://www.hello-nature.com/us/*)
KEYLAN Mn	Rational-designed	Optimizing Manganese uptake and boosting plant metabolism	Hello Nature (*https://www.hello-nature.com/us/*)
KEYLAN Zn	Rational-designed	Optimizing Zinc uptake and boosting plant metabolism	Hello Nature (*https://www.hello-nature.com/us/*)
NOP-1	Rational-designed	Inhibiting plant senescence	[99]
PEP6-32	Rational-designed	Plant seedlings presented longer hypocotyls and diminished cotyledon expansion when grown under red light.	[226]
PSK-α	Rational-designed	Promote cell growth and proliferation	[227]

an alternative approach to controlling pests.[53] Insecticidal peptides with ideal properties are now being considered as the potential alternatives.

Insecticidal peptides act on a variety of pests such as Lepidoptera, Diptera, and Hemiptera. Some reported insecticidal peptides and their functions are summarized in Table 3. Insecticidal peptides are largely derived from animals (63.1%), followed by plants (19.64%) and synthetic peptides (11%) (Fig. 6C). There are few insecticidal peptides from microorganisms, except some fungi and bacteria, such as Destruxin A (DA) secreted by *Metarhizium anisopliae* and longibrachinA-I from *Trichoderma longibrachiatum RIFAI*.

Naturally insecticidal peptides are principally derived from the venom of arthropods (e.g., spiders, scorpions, ants, etc.) and marine animals (e.g., jellyfish,[54–56] anemones,[57–60] cone snails,[61–64] etc.). Spider venoms are an incredible source of disulfide-rich insecticidal peptides. For instance, many insecticidal peptides (e.g., ω-κ-HXTX-HV1A, ω-ACTX-Hv2a, etc.) have been found in the venom of *Hadronyche versuta*. β-Diguetoxin-Dc1a (Dc1a), a toxin from the desert bush spider *Diguetia canities,* incapacitates insect pests but has no toxicity in mammals.[25] NnFV peptide, a marine bioactive substance, is extracted from jellyfish.[56] TxVIA peptide from *Conus textile* contains 27 amino acids and shows insecticidal activity when injected into cabbage moth and house fly larvae.[62] Interestingly, a total of 4782 insect neuropeptide records were identified as performing various related physiological functions (such as development, metabolism, water and ion homeostasis, etc.) for insect survival. Among these neuropeptides, proctolin, insect kinins (IKs), pheromone biosynthesis activating neuropeptide (PBAN) and allatostatins (ASTs) have been studied in detail.[65] These studies pave the way for the generation of novel insect control agents based on backbone cyclic peptidomimetic antagonists of insect-neuropeptides.[65] Vestaron, recent winner of the Green Chemistry award, is leading a 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, spotted-winged drosophila, and spider mites in greenhouse settings and 2) Spear®-Lep was developed to control lepidopteran pests such as caterpillars, worms, and loopers on indoor and outdoor crops. Vestaron also invented Leprotec®, which is a versatile liquid formulation of the lepidopteran active Bt kurstaki strain EVB-113-19 to prevent loopers, worms, and other caterpillars and is an ideal partner for use with Spear®-Lep bioinsecticide.[66] These products were developed to provide growers with novel, effective chemistries that safely kill pests while having no adverse effects on the ecosystem.

Most plant-derived insecticidal peptides, like cyclic peptide, pea albumin, and defense and recombinant peptide[67] come from *Rubiaceae*, *Leguminosae*, *Violaceae*, *Solanaceae*, and *Cucurbitaceae*.[68] More than 47 cyclic peptides from *Clitoria ternatea*[69] exhibited insecticidal effects. PA1b (Pea Albumin 1 subunit b), a peptide containing 37 amino acids, was isolated from the seeds of *Pisum sativum* and shows remarkable insecticidal activity against insects[70] such as cereal weevils, the mosquitoes *Culex pipiens* and *Aedes aegyptii*, and certain species of aphids. The toxin acts by binding to the subunits c and e of the plasma membrane H-ATPase (V-ATPase) in the insect midgut.[71] In 2017, Sero-X®, the world's first plant-cyclopeptide bioinsecticide, was developed by Innovate Ag of Australia.[9] Due to its nontoxic and bee-friendly properties, it is approved for use in cotton and macadamia nut plants in Australia to control *Helicoverpa armigera*, *Bemesia tabaci*, and *Nezara viridula*.[72]

A number of mimic peptides with favorable insecticidal activity[27,35,36,41,45,59,63,67,69–71,73-102] have been obtained by modifying native peptides to overcome bioinstability. Several insect kinin mimics were obtained by introducing unnatural amino acids at the enzymatic site to yield products with remarkably more resistant to enzymatic degradation.[103] We recently discover insect kinin analogues L_{25} and M_1, which

Table 3
Classification and agricultural bioactivity of some insecticidal peptides (Adapted from Ye et al.[120]).

Insecticidal peptides from animals				
Peptide	Source	Function	Species effectiveness	Refs.
AaHIT1	*Androctonus australis*	Insecticidal	*S. litura*	228
AaIT	*A. australis*	Insecticidal	*Heliothis virescens*	229
Adipokinetic hormone	*Locusta migratoria*	Effects of development and ecdysis	*L. migratoria*	230
Allatostatin A, Allatostatin B, Allatostatin C	Cockroach Cricket Moth	Inhibit JH synthesis	Cockroach Cricket Moth	231–233
Allatotropin	*Manduca sexta*	Stimulate JH biosynthesis	*M. sexta*	234
α-nemertides	*Lineus longissimus*	Insecticidal	*Carcinus maenas*	235
Anti-diuretic Factor	*Tenebrio molitor*	Inhibit liquid secretion in malpighian tubules	*T. molitor*	236
Av3	*Anemonia viridis*	Insecticidal	Drosophila	59
Ba1, Ba2	*Brachypelma ruhnaui*	Insecticidal	*Acheta domestica*	237
β-diguetoxin-Dc1a	*Diguetia canities*	Insecticidal	*Blattella germanica*	25
BjαIT	*Buthotus judaicus*	Insecticidal	*Sarcophaga falculata*	238
BmKIT1	*Mesobuthus martensii*	Insecticidal	*Gryllus bimaculatus*	239
BmBKTx1	*M. martensii*	Insecticidal	*D. melanogaster* *Periplaneta americana*	240
BoiTx1	*Buthus occitanus*	Insecticidal	*Drosophila*	241
BotIT1, BotIT2, BotIT4, BotIT5, BotIT6	*B. occitanus*	Insecticidal	*B. germanica*	242–244
Brachyin	*Brachypelma albopilosum*	Insecticidal	*P. americana* *T. molitor*	245
BrhI, BrhV	*Bracon hebetor*	Insecticidal	*Galleria mellonella*	246
BsIT1, BsIT12, BsIT13, BsIT14	*Buthus sindicus*	Insecticidal	*S. falculata* *B. germanica*	247
β-TRTX-Cd1a	*Ceratogyrus darlingi*	Insecticidal	*Lucilia cuprina*	248
Bursicon	*D. melanogaster*	Influence cuticle	*D. melanogaster*	249,250
CCHamide	*Bombyx mori*	Influence feeding	*B. mori*	251
Checacin1	*Chelifer Cancroides*	Insecticidal	*Acyrthosiphon pisum*	252
CNMamide	*D. melanogaster*	–	*D. melanogaster*	253
CpTx1, CpTx2a, CpTx3a, CpTx4a	*Cheiracanthium punctorium*	Insecticidal	*Sarcophaga carnaria*	254,255
CsTx-1, CsTx-2a, CsTx-2b	*Cupiennius salei*	Insecticidal	*D. melanogaster*	256
Ct-IT1, Ct-IT2	*Centruroides tecomanus*	Insecticidal	*A. domesticus*	257
Diuretic Hormone 31	*Diploptera punctata*	Regulate fluid secretion	*D. punctata*	78
GF1	*Anthopleura xanthogrammica*	Insecticidal	*T. molitor*	58
GP2, GP5	*D. melanogaster*	Antidiuresis	*D. melanogaster*	258,259
HWTX-V	*Haplopelma schmidti*	Insecticidal	*Migratory manieusis*	260
ImI	*Conus geographus*	Insecticidal	*T. molitor*	63
J-ACTX-Hv1a, J-ACTX-Hv1b, J-ACTX-Hv1c, ω-ACTX-Hv2a, ω/κ-HXTX-Hv1a	*Hadronyche versuta*	Insecticidal	*A. domesticus*	261,6,262
Kinin	*Leucophaea maderae*	Influence myotropic, diuretic activities	*L.maderae*	100
κ-TRTX-Ec (2a,2 b)	*Eurocratoscelus constrictus*	Insecticidal	*G. bimaculatus*	263
LaSicTox-αIB2bi	*Loxosceles arizonica*	Insecticidal	*A. domesticus*	264
Latroeggtoxin-III	*Latrodectus tredecimguttatus*	Insecticidal	*P. americana*	265
LqhIT2	*Leiurus quinquestriatus*	Insecticidal	*S. litura*	266
LqhαIT	*L. quinquestriatus*	Insecticidal	*S. falculata*	267
Magi2, Magi3	*Macrothele gigas*	Insecticidal	*S.litura* *G. bimaculatus*	268,269
Natalisin	*Drosophila*	Influence reproduction	*Drosophila*	270
Neuropeptide F	*Drosophila*	Influence feeding and foraging	*Drosophila*	271
Neuropeptide-like precursor	*Drosophila*	Regulate development	*Drosophila*	272
NnFV	*Nemopilema nomurai*	Insecticidal	*T. cinnabarinus*	56
OAIP-1	*Selenotypus plumipes*	Insecticidal	*T. molitor* *Helicoverpa armigera*	85
Orcokinin	*B. mori*	Influence gut function	*B. mori*	273
OtTx1	*O. takobius*	Insecticidal	*S. carnaria*	274
Oxki1, Oxki2, Pin2	*Oxyopes kitabensis*	Insecticidal	*S. litura*	275
OxyTx1, OxyTx2	*Oxyopes lineatus*	Insecticidal	*Spodoptera frugiperda*	276
Partner of bursicon	*D. melanogaster*	Influence cuticle	*D. melanogaster*	258,259
Pheromone biosynthesis activating neuropeptide (PBAN)	*L. maderae*	Regulate pheromone biosynthesis	*L.maderae*	277
PnTx4-3, PnTx4 (5-5)	*Phoneutria nigriventer*	Insecticidal	*Musca domestica*	278,279
Poneratoxin	*Paraponera clavata*	Insecticidal	*S. frugiperda*	280
Ponericins	*Pachycondyla goeldii*	Insecticidal	*A. domesticus*	93
RFV	*Rhopilema esculentum*	Insecticidal	*Stephanitis pyri* *A. medicaginis* *Myzus persicae*	55

(*continued on next page*)

Table 3 (*continued*)

RY amide	*Nasonia vitripennis*	–	*N. vitripennis*	89
Sf1a	*Segesteria florentina*	Insecticidal	*L. cuprina*	26
Short neuropeptide F	*Drosophila*	Influence feeding and growth	*Drosophila*	281
Sulfakinin	*L.maderae*	Continued excitement	*L.maderae*	282
TbIT-1	*Tityus bahiensis*	Insecticidal	*M. domestica*	283
Trissin	*D. melanogaster*	Regulate foregut-midgut contractions	*D. melanogaster*	284
TxVIA	*C. geographus*	Insecticidal	*M. domestica*	61
Tx4 (6–1)	*P. nigriventer*	Insecticidal	*P. americana* *M. domestica*	75
U-MYRTX-MANr1	*Manica rubida*	Insecticidal	Aphids	285
U1-TRTX-Ct1 (a,b)	*Coremiocnemis tropix*	Insecticidal	*L. cuprina*	286
U1-liotoxin-Lw1a	*Liocheles waigiensis*	Insecticidal	*T. molitor* *L. cuprina*	287
U2-SCTX-Li1b	*Loxosceles intermedia*	Insecticidal	*L. cuprina*	288
μ-DGTX-Dc1a	*D. canities*	Insecticidal	*H. virescens*	52
μ-NPTX-Nc1a	*Nephila clavata*	Insecticidal	*P. americana*	289
μ-SPRTX-Hv2	*Heteropoda venatoria*	Insecticidal	*P. americana*	290
μ-theraphotoxin-Ae1a	*Augacephalus ezendami*	Insecticidal	*B. germanica*	95
μ-TRTX-Ae1a	*A. ezendami*	Insecticidal	*L. cuprina* *D. melanogaster* *Rhodnius prolixus*	96
μ/ω-TRTX-Mb1a, μ/ω-TRTX-Mb1b	*Monocentropus balfouri*	Insecticidal	*L. cuprina*	291
Vespulakinin	*Vespula maculifrons*	Insecticidal	Cockroach	292
ω -Tbo-IT1	*Tibellus oblongus*	Insecticidal	*M.domestica* *Gromphadorhina portentosa*	293
δ-PaluIT1, δ-PaluIT2, δ-PaluIT3, δ-PaluIT4	*Pireneitega luctuosa*	Insecticidal	*S. litura*	294
Insecticidal peptides from plant				
BrD1	*Brassica rapa*	Insecticidal	*Nilaparvata lugens*	295
Cter M	*Clitorea ternatea*	Insecticidal	*H. armigera*	296
CycloviolacinH3, CycloviolacinO1, CycloviolacinO2, CycloviolacinO3, CycloviolacinO8, CycloviolacinO12, CycloviolacinO13, CycloviolacinO14, CycloviolacinO15, CycloviolacinO16, CycloviolacinO19, CycloviolacinO24, CycloviolacinY1, CycloviolacinY4, CycloviolacinY5	*Viola odorata*	Insecticidal	*M. persicae* *Pomacea canaliculata* *Trichostrongylus colubriformis* *Hemonchus contortus*	297–299
Hypa A	*Hybanthus parviflorus*	Insecticidal	*Ceratitis capitata*	300
Jaburetox-2Ec	*Canavalia ensiformis*	Insecticidal	*Dysdercus peruvianus* *Callosobruchus maculatus* *S. frugiperda*	300
KalataB1, KalataB2, KalataB6 KalataB7, KalataB8	*Oldenlandia affinis*	Insecticidal	*H. armigera* *P. canaliculata* *H. contortus* *T. colubriformis*	301,299,296
Parigidin-Br1	*Palicourea rigida*	Insecticidal	*Diatraea saccharalis* *S. frugiperda*	302
PA1b	*Pisum sativum*	Insecticidal	*Sitophilus oryzae* *Sitophilus granarius* *Sitophylus zeamays* *Culex pipiens* *A.pisum* *Aedes aegypti*	71,73,82
Sero-X®	*C. ternatea*	Insecticidal	*H. armigera* *Bemesia tabaci* *Nezara viridula*	72
Varv A, Varv E, Kalata S	*V. odorata*	Insecticidal	*H. contortus* *T. colubriformis*	297
Vhl-1	*V. hederacea*	Insecticidal	*H. contortus* *T. colubriformis*	297
VrCRP	*Vigna radiata*	Insecticidal	*Callosobruchus chinensis*	303
VrD1	*V. radiata*	Insecticidal	*Bruchidae*	304
Insecticidal peptides from microorganism				
Beauveriolide I	*Beauveria bassiana*	Insecticidal	*S. litura* *C. chinensis*	305
Cyclic depsipeptides	*Marine fungi*	Insecticidal	*S. litura* *C. chinensis*	306
Cyclodipeptides	*Marine fungi*	Insecticidal	*Helicoverpa zea*	307
Destruxins	*Metarhizium anisopliae*	Insecticidal	*Lepidoptera Homoptera* *Diptera* *Orthoptera*	308
Iso-isariin D	*B. bassiana*	Insecticidal	*Artemia salina*	309

(*continued on next page*)

Table 3 (*continued*)

Longibrachin A-I, Longibrachin A–II–b	*Trichoderma longibrachiatum RIFAI*	Insecticidal	*Calliphora vomitoria*	310
Pumilacidin C	*Marine bacteria*	Insecticidal	*A. aegypti*	311
SLP1	*Streptomyces laindensis H008*	Insecticidal	*Lipaphis erysimi*	312
Others				
CAPA-PK analogue (1895 + 2315)	CAPA-PK analogue	Insecticidal	*M. persicae*	313
GS-ω/κ-HXTX-Hv1a	Genetic engineering	Insecticidal	Aphids Hrips Delphacidaes	6
H17	Allatostatin mimic	Insecticidal	*D. punctata*	314
K-Aib-1	Kinin mimic	Insecticidal	*A. pisum*	315
K15, K24, P5, B1, II12, A6	Allatostatin mimic	Insecticidal	*D.punctata*	5,316–319
Manse-AT	Allatotropin	Insecticidal	*M. sexta*	102
Manse-AT (10–13)	Allatotropin	Insecticidal	*M. sexta*	320
PPK-Jo	Kinin analogues	Insecticidal	Moths	321
II-1, IV-3, M1,L25, L7	Kinin mimic	Insecticidal	*Aphis glycines*	7,104,322,323
2460 analogue	Kinin analogues	Insecticidal	*M. persicae*	324
1963 analogue	Diapause hormone analogue	Insecticidal	*H. zea*	325

exhibit excellent aphicidal activity and low toxicity to bees.[104] The discovery of these peptide-mimic compounds offers a novel strategy to create new green pest control agents.

4.4. Herbicidal peptides

In general, weeds produce the highest potential loss (34%), comparing with insect pests and pathogens (losses of 18% and 16%). Weed control can be managed mechanically or chemically, and thus bring about higher efficacy than the control of animal pests or diseases.[105] Traditional herbicides contribute to ensuring crop yield, but the high dependence on them has led to adverse effects, such as residues in crops and the environment. Therefore, the need for new eco-friendly herbicides is growing.[106] Some herbicidal peptides and their functions are summarized in Table 4. They primarily come from microorganisms (43.75%), followed by plants (37.50%) and synthetics (18.75%) (Fig. 6D).

Naturally occurring and synthetic peptides have been considered as promising herbicidal tools with applications in crop protection. Bialaphos is a tripeptide separated and purified from the fermentation broth of *Streptomyces hygroscopicus*.[106] Thamatomin A comes from *Streptomyces acidiscabies*. Some herbicidal peptides are found in plants, such as five dipeptides and one pentapeptide from hydrolysate of corn gluten meal.[107–109]

As shown in Table 4, these peptides are active against a wide range of weeds. For instance, Romidepsin has effects on *Amaranthus palmeri* L. and *Sinapsis arvensis* L.. Ala-Ala functions against *Lolium perenne* L. Tentoxin, a cyclic tetrapeptide from *Alternaria tenuis*, inhibits cyclic photosynthetic phosphorylation and energy transfer, leading to seedling chlorosis in weeds while having no effect on soybean and corn. The peptide can also be used with herbicides to promote opening of the weed stomata under adverse circumstances, thus enhancing drug absorption by the weeds and making them wither more quickly.

Two peptides have been commercially developed into peptide herbicides. Bialaphos (https://www.company-histories.com/Meiji-Seika-Kaisha-Ltd-Company-History.html), a tripeptide herbicide developed by Japan Meiji Seika Kaisha, is mainly used to control a variety of annual and perennial monocotyledon and dicotyledon weeds in grape, apple, citrus gardens as well as nontillage and uncultivated fields. Bialaphos itself has no herbicidal activity, but its degradation products glyphosate and alanine, have herbicidal activity on weeds. Thaxomin A, the active ingredient of Opportune™ (https://marronebio.com/) developed by Marrone Bio Innovation, is a unique inhibitor of cellulose synthesis. In 2013, it was approved as a pollution-free biological herbicide for weed control in rice and other grain fields by the United States Environmental Protection Agency.

5. Challenges and prospects on peptide-based agrochemicals

5.1. Challenges

Despite the fact that peptides have been successfully used in plant protection, they still face several challenges because of shortcomings such as low systemic stability, negligible oral activity, and high cost of production. Generally, natural peptides are easily degraded by enzymes in the organism and affected by external environmental conditions such as light and pH, resulting in poor stability and low bioavailability. Unlike peptide-based drugs, peptide pesticides that are too costly will be of limited acceptance in the commercial market. Therefore, to make peptide-based agrochemicals acceptable, they must have better stability, bioactivity, and lower cost.

5.2. Prospects in peptide-based agrochemicals

5.2.1. Performance optimization on structure and formulation

Improving the stability and bioavailability of natural peptides are important goals in the discovery of new peptide-based drugs and agrochemicals. Structural optimization and suitable formulation of natural peptides can yield more acceptable peptides or their mimics, and peptide products with better bioavailability can also be achieved by delivery system optimization.

5.2.1.1. Structural optimization. To overcome the hurdles of low stability and weak activity of natural peptides, several methods of structural optimization, including amino acid substitution, cyclization strategies, mimic design, etc., have been developed.[9,110] Natural peptides can be modified by genetic engineering to obtain novel peptides with desired properties. For example, the bioinsecticide Spear® was developed by using genetic engineering to add a glycine-serine dipeptide to ω/κ-HXTX-Hv1a, the natural spider venom peptide. This product has higher activity, lower risk, and more persistence than the natural product, and is considered a sustainable and effective green tool for pest control in agriculture and public health.[111]

5.2.1.2. Formulation. Designing different formulations, such as suspension agent, microemulsion, and capsule suspension, can protect peptide molecules from degradation by environmental factors such as water, UV, temperature, and metabolic enzymes. This not only enhances stability

Table 4
Classification and agricultural bioactivity of some herbicidal peptides.

Peptide	Source	Function	Species effectiveness	Refs.
Herbicidal peptide from Plants				
Ala-Ala	*Z. mays* L.	Herbicidal	*Lolium perenne* L.	109
Ala-Asn	*Z. mays* L.	Herbicidal	*L. perenne* L.	107
Ala-Gln	*Z. mays* L.	Herbicidal	*L. perenne* L.	107
Gly-Ala	*Z. mays* L.	Herbicidal	*L. perenne* L.	107
Gln-Gln	*Z. mays* L.	Herbicidal	*L. perenne* L.	107
Leu-Ser-Pro-Ala-Gln	*Z. mays* L.	Herbicidal	*L. perenne* L.	108
Herbicidal peptide from microorganisms				
AMPB-Ala-Ala-AMPB	Actinomycetes	Herbicidal	Weed	106
AMPB-Gly-Ala	Actinomycetes	Herbicidal	Weed	106
Basta	*Streptomyces viridochromogenes*	Herbicidal	Weed	326
Bialaphos	Actinomycetes	Herbicidal	Weed	106
Compounds 1-7	*Bacillus clausii* DTM1	Herbicidal	*Poa annua* L.	83
des-N^2-methylthaxtomin C	*S. scabies*	Herbicidal	*Agrotis palustris*	106
Herbiace	*S. viridochromogenes*	Herbicidal	Weed	326
Hydroxythaxtomin A	*S. scabies*	Herbicidal	*Lemna minor*	106
Hydroxythaxtomin C	*S. scabies*	Herbicidal	*L.minor*	106
Phosalacine	Actinomycetes	Herbicidal	Weed	106
Plumebmycin A	Actinomycetes	Herbicidal	Weed	106
Plumebmycin B	Actinomycetes	Herbicidal	Weed	106
Resormycin	*Streptomyces platensis* MJ953-SF5	Herbicidal	Dicotyledonous weeds	106
Romidepsin	*Burkholderia rinojensis*	Herbicidal	*Amaranthus palmeri* L. *Sinapsis arvensis* L. *Amaranthus tuberculatus(Moq.) Sauer* *Trifolium repens* L. *Conyza canadensis* L. *Bassia scoparia* L. *Stellaria media (L.) Vill.* *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.*	327
Tentoxin	*Alternaria tenuis*	Herbicidal	Weed	328
Thaxtomin A	*S. scabies*	Herbicidal	*L. minor* *A. palustris*	106
Thaxtomin A o-isomer	*S. scabies*	Herbicidal	*L.minor* *A. palustris*	106
Thaxtomin A p-isomer	*S. scabies*	Herbicidal	*A. palustris*	106
Thaxtomin B	*S. scabies*	Herbicidal	*A. palustris*	106
Thaxtomin C	*S. scabies*	Herbicidal	*L.minor*	106
triaphos	Actinomycetes	Herbicidal	Weed	106
Others				
Compounds 14,15	Synthesis	Herbicidal	Weed	329
5a	Synthesis	Herbicidal	Barnyard Grass Crabgras	330

but also improves bioavailability because these formulations can easily enter the body through the epidermis to reach the target site.[111] For example, the rainfast amphiphilic peptide thanatin (THA) tightly anchors AMP dermaseptin 01 (DS01) to the surface of soybean leaves upon spray application. A fusion of the antimicrobial peptides DS01 and THA (DS01-THA) inhibits germination of *P. pachyrhizi* spores in vitro and reduces Asian soybean rust disease.[112] In addition, peptide formulates mixed with chemical pesticides via different mechanisms can expand the activity spectrum and delay resistance.[81,113] Hexapeptides PAFs are capable of inhibiting fungi that are unaffected by frequently used fungicides (as Alternaria sp.).[113] 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.[81]

5.3. Delivery system

Drug delivery systems (DDS) can deliver an appropriate amount of drugs to their target through controlled release technologies such as hydrogels, cubosomes, and nanocarriers, which increase drug utilization efficiency.[114,115] The easily degradable peptides in combination with new DDS strategies can be used for precision agriculture. Nakasu et al. infused insecticidal peptides into plant lectin or viral coat protein improving utilization rate and insecticidal activity.[116] Herzig et al. delivered insecticidal toxins through transgenic entomopathogens, such as baculovirus, the *Bacillus thuringiensis* soil bacterium, or the Metarhizium fungus. These pathogens can infect insects while simultaneously expressing the insecticidal toxin, thereby producing synergistic insecticidal effects.[94]

5.4. Biosynthesis of peptides

Peptides are commonly prepared through chemical synthetic methods of “liquid phase synthesis” and “solid phase synthesis.” However, chemical synthesis is expensive and limited in large-scale production. Therefore, many studies seek to obtain peptides more economically. Biosynthesis of peptides via enzymatic, fermentation, and genetic

engineering methods is favored for its advantages such as wide availability of raw materials and low cost.[117] The heterologous systems currently used for peptide production include bacteria (e.g., *E. coli* and *B. subtilis*), fungi (e.g., *Pichia pastoris* and *Saccharomyces cerevisiae*), plants (cells and tissue cultures), and related strategies for reaching greater functional peptide production.[118,119] For example, cyclic peptides are obtained from biosynthesis in fungi, bacteria, and plants.[118] Spear®, with a cost almost equivalent to that of traditional insecticides, is produced by fermentation of *Kluyveromyces lactis*.[6] Therefore, preparing peptide agrochemicals by biosynthesis is worthy of further study.

6. Conclusion and outlook

The last 120 years have witnessed the emergence of peptides and rapid development of peptide-based drugs and agrochemicals in a global trend to seek products with high efficiency, low toxicity, and environmental safety. The field of peptide agrochemicals is maturing in several aspects, including long-term and extensive research on the application, production, and discovery of numerous agricultural peptides as potential candidates in farming. Several encouraging technologies of structure optimization and formulation, delivery systems, and biosynthesis will continue to contribute to the growth of peptide agrochemicals.

Peptides that meet the requirements of high efficiency and safety are beneficial to plant protection in eco-agriculture. The industrialization of peptides will be accelerated by rapid development of molecular biology, biochemistry, synthetic biology, and genetic engineering. In addition to X-ray crystallography, it is now possible to obtain 3D structures of proteins by AlphaFold2, RoseTTAFold, and other new methods (phage peptide library, mRNA display, virtual screening) can be used to predict useful peptide ligands. Studying the interaction between proteins and ligands is of great value for drug design. The designed peptides have a high targeting affinity, meaning that a very small amount of peptide is sufficient to control weeds, pathogens, and insects. The cost may be more competitive than existing pesticides due to the low dosage when peptides are completely or partially fermented. Peptides will likely become mainstream tools for plant protection in the future. Given the fact that peptides are developing quickly, this review could not describe and discuss all aspects of peptides as new tools for plant protection in eco-agriculture. However, we hope to draw the attention of biochemists, molecular biologists, and agronomists to this new area to promote a more detailed and in-depth study on peptide-based agrochemicals for the sustainable development of green agriculture.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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