

The invisible hand shaping plants: Explore the applications, challenges, and ecological prospects of plant growth regulators

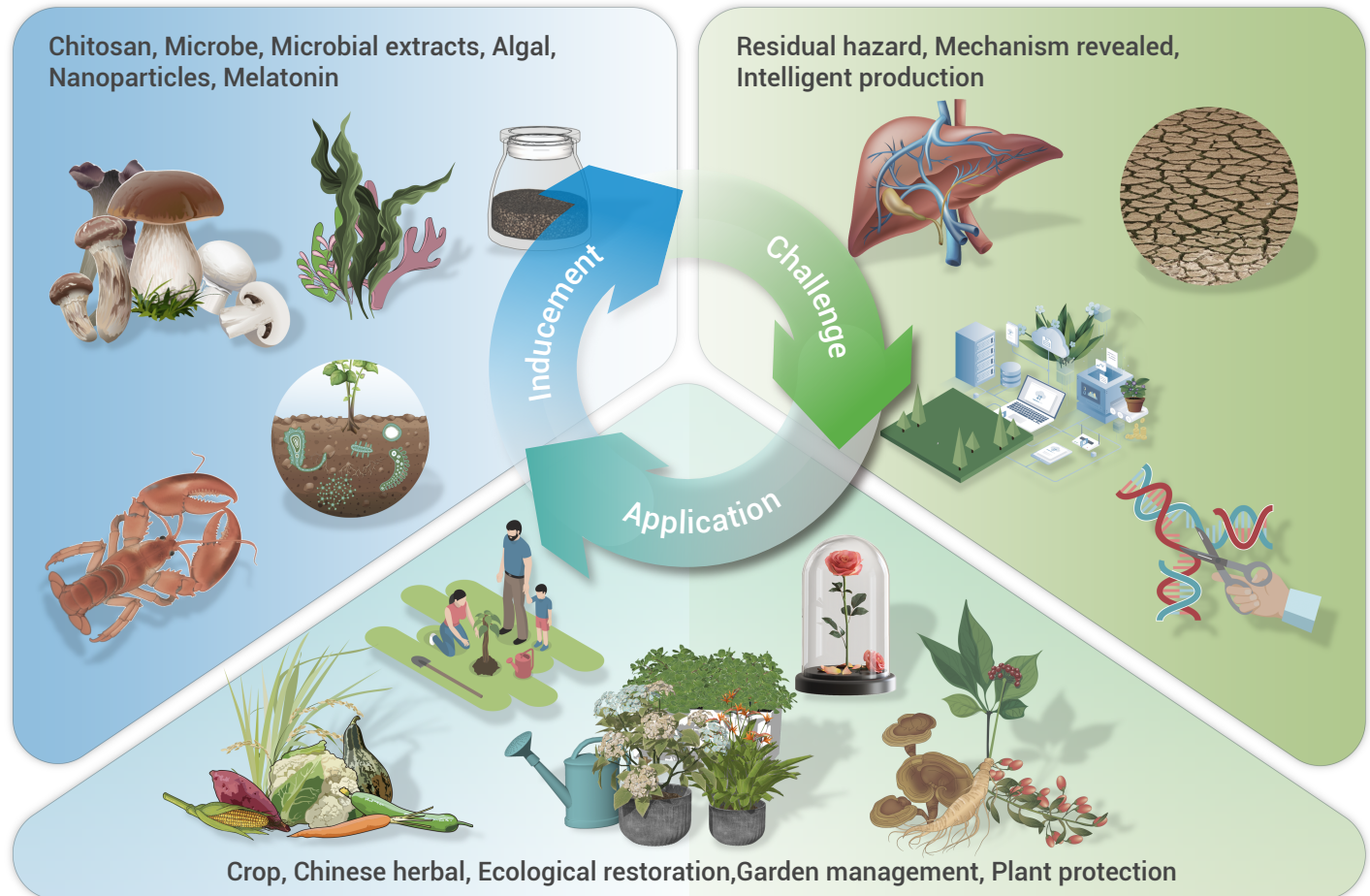
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Received: June 9, 2025; Accepted: October 21, 2025; Published Online: November 12, 2025; <https://doi.org/10.59717/j.xinn-life.2025.100170>

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GRAPHICAL ABSTRACT



PUBLIC SUMMARY

- Plant growth regulators (PGRs) create a new model for regulating plant growth.
- PGRs are widely applied in agriculture, horticulture, medicinal herbs, and ecological restoration.
- Challenges: safety, mechanism study, and new formulation development.
- Promote biopesticides over pesticides, enhance PGRs' role in phytoremediation.

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Received: June 9, 2025; Accepted: October 21, 2025; Published Online: November 12, 2025; <https://doi.org/10.59717/j.xinn-life.2025.100170>

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Citation: Liu Y., Hu Y., Kong M., et al. (2025). The invisible hand shaping plants: Explore the applications, challenges, and ecological prospects of plant growth regulators. *The Innovation Life* 3:100170.

In the past two decades, research on plant growth regulators has developed rapidly. The year 2020 marked an important milestone, as the number of research papers published in this field exceeded 1,000 for the first time, and the number of papers continued to grow exponentially thereafter. However, in this vigorous development process, a comprehensive and accurate overview of this field is particularly lacking. Our review aims to fill this gap and provide a panoramic view of the rapidly developing field of plant growth regulation. We will comprehensively analyze the research progress and applications of plant growth hormones and plant growth regulators from multiple key areas. Our narrative spans the historical origins of plant growth regulators and their transformative impacts across various fields, along with the economic and ecological effects they bring, including agriculture, horticulture, environmental protection, and plant breeding. Additionally, we discuss the potential applications and challenges associated with plant growth regulators. Looking ahead, we cautiously anticipate further advancements in the field of plant growth regulator research, particularly in conjunction with gene editing technologies and smart agriculture. This review paper aims to provide a comprehensive reference framework for researchers, agricultural workers, and related industries, helping them better understand the fundamental principles and practical applications of plant growth hormones and regulators, thereby promoting further research and development in this field. Through systematic analysis and summarization, we hope to provide a theoretical foundation and practical guidance for future studies, facilitating the sustainable development of plant production.

INTRODUCTION

Plant growth regulators (PGRs) can be defined as naturally occurring or synthetic compounds which affect metabolic, growth, and developmental processes in higher plants.¹ Nowadays, a significant number of researchers refer to strains that can produce bioactive substances and influence plant growth, such as plant growth-promoting bacteria (PGPB), as a type of plant growth regulator.²⁻⁴ In 1928, the first plant hormone, auxin, was isolated on an international scale. Subsequently, scientists began to apply artificially synthesized auxin analogs, such as indoleacetic acid (IAA) and naphthylacetic acid (NAA), in practices aimed at promoting root development in plant cuttings. With the discovery of other plant hormones and the continuous verification of their functions, scientists have successively artificially synthesized a variety of plant growth regulators (PGRs), which have been widely applied in various purposes such as increasing crop yields and improving crop quality. Plant growth regulators have a wide range of applications, including increasing crop yields, horticultural management, and plant breeding. The application of plant growth regulators in modern agriculture and horticultural management not only enhances crop yields and quality but also strengthens plants' resistance to adverse conditions, optimizes plant management, promotes sustainable development, and boosts scientific research and economic benefits. However, the application of PGRs faces several challenges due to the lack of fundamental understanding among farmer households, including the safety hazards of residual PGR, issues of compliance and supervision, and difficulties in accurately grasping the methods and dosages of application.

Therefore, integrating artificial intelligence to accelerate the development and utilization of high-quality PGR can enhance the efficacy of novel plant regulators in improving crop resistance to viruses, pests, and environmental stress, thus reducing the physiological toxicity and negative impacts of these substances. Looking ahead, we anticipate that the application of PGRs in ecological restoration projects will significantly enhance the efficiency of plant remediation, help overcome challenges related to the survival, establishment, and proliferation of plants within ecosystems, thereby promoting the overall health and stability of ecosystems. Therefore, this review not only discusses the current landscape of plant growth regulators but also provides a forward-looking perspective on their profound implications in the field of future ecological restoration.

PLANT GROWTH REGULATORS HISTORY

In 1880, Charles Darwin and Francis described the existence of a medium that regulates the curvature of seedlings towards a light source.⁵ In 1926, the biologist Frits Went first discovered the key substance that affects the phototropism of plants and named it "auxin".⁶ The discovery of auxin has provided an important theoretical basis for understanding how plants respond to environmental changes and regulate growth. It has also opened up a new field in plant physiology and advanced the development of agricultural and horticultural technologies. Following the publication of his research findings, there was widespread attention, prompting other scientists to further explore the properties, synthesis mechanisms, and roles of auxins in plant growth and development (Figure 1).⁷⁻⁹

In 1926, gibberellin (GA) was first isolated by Hori from the fungal plant pathogen *Gibberella fujikuroi*, which is characterized by causing excessive elongation of seedlings, leading to lodging and sterility in rice. After the 1950s, scientists studied the chemical structure of gibberellins and eventually determined their molecular structure.¹⁰ Subsequently, more types of gibberellins were discovered, including GA₁, GA₃, etc., and it was confirmed that they had different biological activities and mechanisms of action.¹¹ The functions of gibberellin in the plant growth process have been continuously explored, such as promoting seed germination, promoting fruit enlargement, and influencing stem elongation. Their applications in agriculture have also become increasingly widespread, for instance, by applying gibberellin to promote crop growth, increase yield or improve fruit quality (Figure 1).¹²⁻¹³

In 1950, scientists observed that certain substances could promote plant cell division during the process of plant tissue culture.¹⁴ In 1955, scientists discovered a substance in the root tips of corn that could promote cell division. Through further separation and extraction, this substance was named "cytokinin".¹⁵ In the 1960s, researchers successfully isolated several types of cytokinins, including zeatin and kinetin.¹⁶ The discovery and research of these cytokinins greatly advanced the development of plant physiology. Scientists have recognized the importance of cytokinin in plant growth, development, and response to environmental stress. The application scope of cytokinins gradually expanded to areas such as tissue culture, plant propagation, and crop yield increase.

In the 1960s, botanist Ohkuma and colleagues first observed that plants produce a substance under certain conditions that leads to the shedding of leaves and fruits. Named "abscisic acid (ABA)" due to its role in the abscission

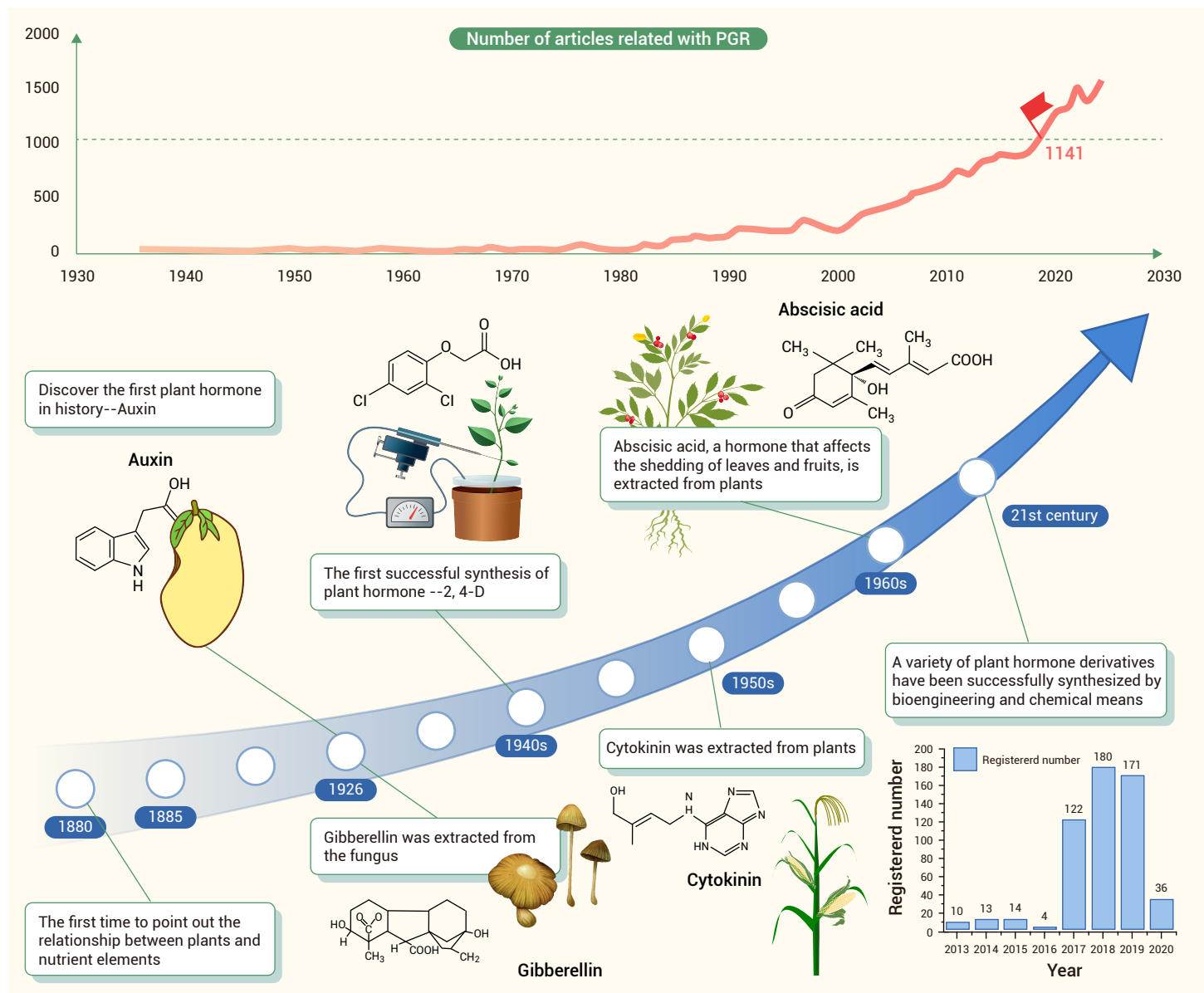


Figure 1. A review of the historical development of plant growth regulators.

of plant leaves and fruits, this compound is closely associated with these processes.¹⁷ The discovery of ABA is an important milestone in the development of plant physiology, marking a deeper understanding of the mechanisms regulating plant growth. Through the research on ABA, scientists not only revealed how plants respond to environmental stress, but also provided a theoretical basis and practical guidance for the sustainable development of modern agriculture (Figure 1).

In 1941, scientists made a significant breakthrough in the research of synthetic plant growth regulators. The first synthetic auxin, 2,4-dichlorophenoxyacetic acid (2,4-D), was used for controlling weed growth. By mimicking the action of natural auxins, it promotes excessive growth and division of plant cells, leading to growth disorder in weeds and thus effectively killing them.¹⁸⁻¹⁹ Following the successful development of 2,4-D, more synthetic plant growth regulators were subsequently developed, including BA, GA₃, 6-BA, FP, GA_{4/7}, and Paclobutrazol, etc. These synthetic substances have played an important role in promoting plant growth, regulating flowering, and fruit development. The introduction of 2,4-D, not only brought significant benefits to agriculture but also provided new tools and perspectives for research in plant physiology. Since then, the research and application of synthetic plant growth regulators have continued to evolve, profoundly impacting crop yield improvements and agricultural production methods (Figure 1).

In the 21st century, scientists have revealed the signaling pathways of

plant hormones and their regulatory mechanisms on gene expression, marking in a new stage of research. Utilizing biotechnology and chemical synthesis methods, researchers have successfully synthesized various derivatives of natural plant hormones (such as auxins and gibberellins), which demonstrate enhanced effects in regulating plant growth.²⁰ During this period, the emergence of gene editing technologies has enabled scientists to regulate the synthesis and signal transduction of plant growth hormones more precisely.²¹⁻²² Nowadays, the application fields of plant growth regulators are continually expanding, encompassing agriculture, horticulture, ecological restoration, and plant breeding. The global plant growth regulators market size was valued at USD 4.67 billion in 2024. The market is projected to grow from USD 5.18 billion in 2025 to USD 11.50 billion by 2032 at a CAGR of 12.08% during the 2025-2032 forecast period.²³ As a major agricultural country, China's demand for genetically modified crops is growing each year. As of the end of March 2020, there were 1,104 effective registered plant growth regulator products in China. Among these, active pharmaceutical ingredients accounted for 4.06% (193 types) of all registered pesticide active ingredients, while formulations represented 2.48% (911 types) of all registered pesticide formulations. This indicates that the plant growth regulator industry holds vast prospects and development potential, both in China and globally (Figure 1).

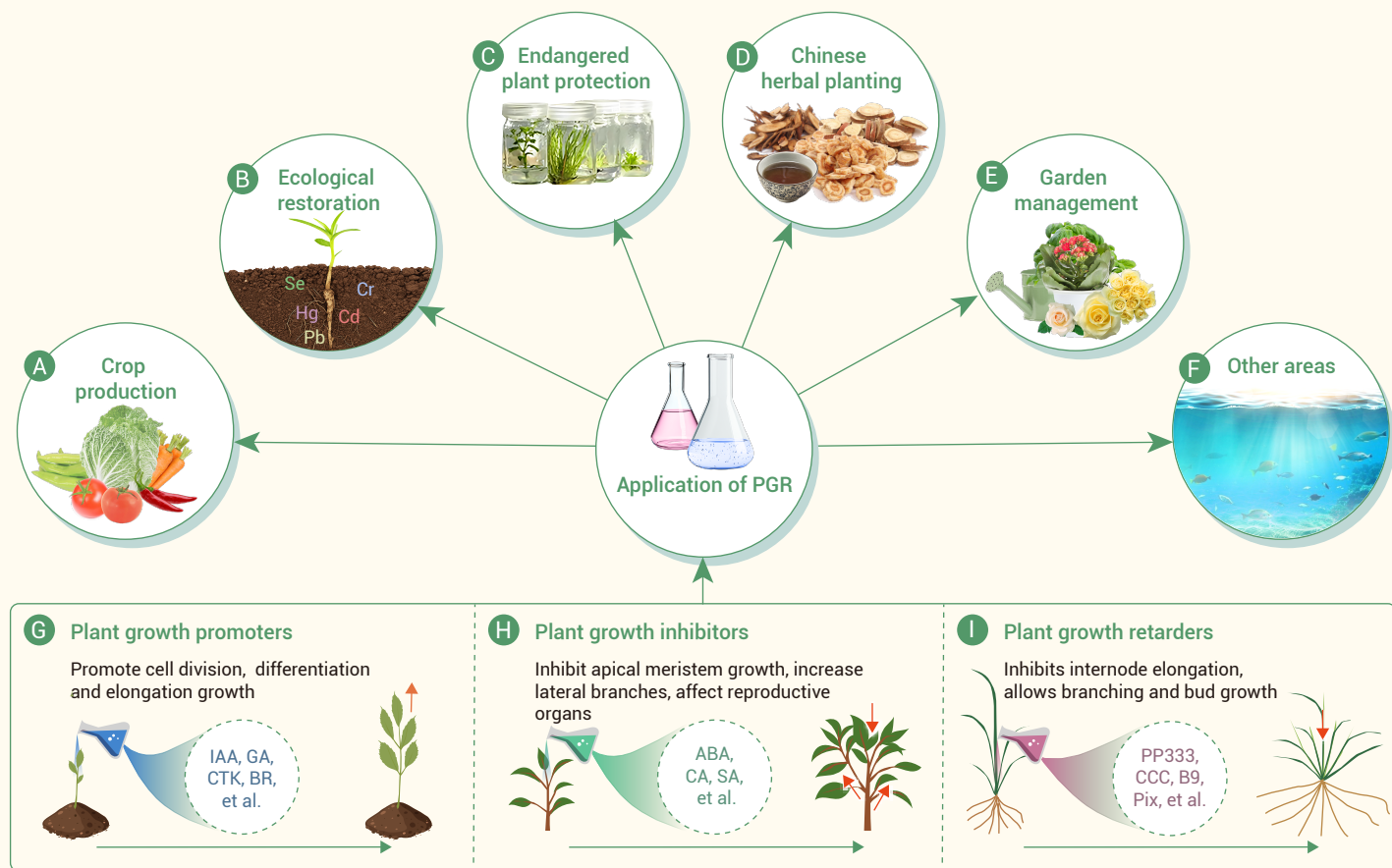


Figure 2. Classification and application of plant growth regulators.

CLASSIFICATION OF THE FUNCTIONS OF PLANT GROWTH REGULATORS

Plant growth regulators is a general term that can exhibit significant variations in their effects on plant growth, depending on the type of regulator and its application concentration. Based on their different roles in plant growth, they can typically be divided into three main categories: Growth promoters, which include low concentrations of auxins, low concentrations of gibberellins, cytokinins, and resinoid sterols; plant growth inhibitors, represented by compounds such as cinnamic acid, coumarin, abscisic acid, and salicylic acid; plant growth retardants, which include substances like chlormequat, paclobutrazol (PP333), and ancymidol.²⁴ (Figures 2G-I).

Plant growth promoter

Plant growth promoters are regulators that can enhance cell division, differentiation, and elongation in plants (Figure 2G). Synthetic growth promoters can be categorized into auxins, gibberellins, cytokinins, brassinosteroids, and polyamines. Auxins accelerate cell division and growth, induce cell division, and alter flowering and fruiting patterns in plants. Among them, naphthaleneacetic acid (NAA) is the most commonly used growth hormone, often used in conjunction with cytokinins to induce stem elongation and root development.²⁵ Gibberellins have multiple functions, including breaking seed dormancy, accelerating cell elongation and growth, promoting flowering of long-day plants under short-day conditions, and preventing organ abscission.²⁶ Cytokinins promote cell division, delay plant senescence, enhance fruit set, and eliminate apical dominance by promoting lateral bud growth.²⁷ Compared to other plant hormones, brassinosteroids are a relatively new class of plant growth promoters that modulate plant stress resistance and endogenous hormone levels, alter the chemical composition of tissues and cells, and induce various enzyme activities to activate unique resistance mechanisms in plants against external stressors.²⁸

Plant growth inhibitor

Plant growth inhibitors are regulators that suppress the growth of apical meristems, resulting in the loss of apical dominance and an increase in the number of lateral branches, thereby affecting the development of reproductive organs (Figure 2H). This inhibitory effect directly prevents the synthesis of nucleic acids and proteins in the cells of the shoot apical meristem, meaning that exogenous gibberellins do not reverse this suppression, while exogenous auxins are effective. Natural plant growth inhibitors include abscisic acid, cinnamic acid, coumarin, and salicylic acid.²⁹⁻³² There are two synthetic inhibitors: TIBA (2,3,5-triiodobenzoic acid) and maleic hydrazide.³³⁻³⁵ Abscisic acid (ABA), as a typical plant growth inhibitor, plays a crucial role in plant stress resistance by inducing drought tolerance, cold tolerance, and salinity resistance.³⁶ Negin et al. explored the effects of abscisic acid (ABA) on plant growth and flowering, revealing its complex role in plant development; it can inhibit early growth and flowering without affecting photosynthesis.³⁷

Plant growth retarder

Plant growth retardants can inhibit internode elongation, resulting in shorter plants while still allowing for branching and apical bud growth (Figure 2I). They do not affect the formation of leaves, flowers, or fruits, thus maintaining the overall morphology and leaf count of the plants. The distinction between growth inhibitors and plant growth retardants lies in whether their effects can be reversed by gibberellins, the effects of growth retardants can be reversed by gibberellins. Common plant growth retardants include PP333, paclobutrazol, B9, and uniconazole (PIX). The application of plant growth retardants on crops such as barley can effectively regulate plant height, delay reproductive growth, and reduce the accumulation of dry matter.³⁸ Growth retardants have been used as anti-lodging agents, reducing stem elongation by blocking gibberellin biosynthesis without compromising yield. In certain crop cultivation processes, the application of plant growth retardants can enhance lodging resistance, decrease the lodging rate, and

Table 1. The application of plant growth regulators in various fields.

Application area	Plants	Plant growth regulator	Effects	References
Horticultural management	Arabidopsis	Guvermectin	Induce flowering	56
	Cucumber; Tomato; Lettuce	Arbuscular mycorrhizal fungi	Increase tolerance to abiotic stress (induce hormone synthesis)	61
	Tomato; Pea	Strigolactone	Inhibition of shoot branching; Promote meristem maturation and flower development	63
	Tomato; Lettuce	Bacillus thuringiensis	Facilitate seed germination and early plant growth	62
Cultivation of chinese medicinal herbs	<i>Dendrobium spp.</i>	Abscisic acid; Salicylic acid; Zeatins	Increase key active ingredients in traditional chinese medicine	69
	<i>Dendrobium officinale</i>	Salicylic acid; Indole-3-acetic acid; Zeatin; abscisic acid	Enhance stem growth and fresh weight of medicinal materials	70
	<i>Gloriosa superba L.</i>	Indole-3-acetic acid; 2,4-dichlorophenoxy; N6-benzyladenine	Boost synthesis of secondary metabolites and promote tissue regeneration	71
	<i>Salvia miltiorrhiza</i>	Jasmonates; Absciscic acid; Gibberellins; Salicylic acid; Cytokinins	Raise levels of hydrophilic phenolic compounds and lipophilic diterpenoid quinones	72
	Marigold	Salicylic acid	Promote growth and flowering; Increasing flavonoid content	73
Conservation of endangered plants	<i>Eryngium maritimum L.</i>	6-benzylaminopurine; Meta-tooling; N6-(2-isopentyl)adenine; Zeatin; Kinetin; IAA	Enhance the proliferation and rooting of axillary buds	94
	<i>Glochidion chodoense C. S. Lee & H. T. Im</i>	2,4-dichlorophenoxy; N6-benzyladenine	Inhibit browning of callus tissue	85
	<i>Helianthus verticillatus (Asteraceae)</i>	N6-benzyladenine; Alpha-naphthalene acetic acid	Enhance the regeneration ability of adventitious buds and increase the yield of adventitious shoots	86
	<i>Tetragstigma hemsleyanum</i>	N6-benzyladenine; Alpha-naphthalene acetic acid	Induce callus tissue to form multiple adventitious buds	87
	<i>Lachenalia viridiflora</i>	N6-benzyladenine; Alpha-naphthalene acetic acid	Promote the regeneration of tuber explants and increase biomass	88
	Arabidopsis	CLE25 peptide	Enhance resistance to dehydration stress	90
	<i>Polygonatum cirrhifolium (Wall.)</i>	IAA; IBA; NAA	Improve vegetative growth in apical rhizome sections	89
Enhance the efficacy of phytoremediation	<i>Brassica napus L.</i>	Triaccontanol	Reduce cadmium-induced oxidative damage	94
	<i>Amaranthus hypochondriacus L.</i>	Indole-3-butyric acid; Diethyl aminoethyl hexanoate	Enhance chlorophyll, antioxidant enzyme activity, and biomass under cadmium stress	95
	<i>Brassica napus L.</i>	Microbacterium oxydans JYC17; Pseudomonas thivervalensis Y1-3-9; Burkholderia cepacia J62	Boost antioxidant enzymes and non-enzymatic antioxidants, reducing oxidative stress	96
	Arabidopsis; Rice; Leaf mustard	Brassinosteroids; Melatonin; Strigolactones	Activate antioxidant genes under heavy metal stress, improving photosynthesis and metabolism	98
	Maize	Gibberellic acid; Aspartate diethoxysuccinic acid	Increase antioxidant activity and total biomass in cadmium-stressed plants	99

help achieve stable crop yields.³⁹⁻⁴⁰

APPLICATION OF PLANT GROWTH REGULATORS

As the role of plant growth regulators in the growth and development of plants is gradually being explored, various challenges have emerged in the extraction and application of endogenous plant hormones, such as poor stability, difficulty in concentration control, uneven physiological effects, and high extraction costs. Consequently, some novel plant growth regulators have been developed, demonstrating numerous advantages over traditional endogenous plant hormones in terms of stability, precise control, adaptability, and cost-effectiveness, which led to the widespread application of plant growth regulators in an increasing number of fields (Figures 2A-F & Table 1).

Crop production

Modern crop production often faces various stresses, such as high salinity, drought, low temperatures, and heavy metals, which can severely impact plant growth and development.⁴¹⁻⁴² It's shown that up to 45% of farmland worldwide is facing water scarcity, and approximately 38% of the population is affected by salinity stress in crop production.⁴³ Reports indicate that the decline in global crop yield due to abiotic stress has reached over 50%.⁴⁴ Researchers are currently focused on developing modern methods to mitigate the hindrances posed by these abiotic stresses on crop production.

Plant growth regulators (PGRs) play a crucial role in regulating signal transduction and interactions with metabolites in plants, which enables PGRs to enhance plant tolerance to various environmental stresses either directly or indirectly.⁴⁵⁻⁴⁶ The potential roles of PGRs, such as auxins, cytokinins, gibberellins, abscisic acid (ABA), ethylene, and salicylic acid have been extensively studied in plant growth regulation and the alleviation of abiotic stresses. Brassinolide is a very small amount of endogenous plant growth regulator isolated from plants in the 1970s.⁴⁷ Brassinolide plays an indispensable role in plant cell expansion, cell division, plant growth, and seed germination.⁴⁸⁻⁴⁹ Recent findings suggest stress-impact mitigating roles of BRs and associated compounds in various plants subjected to various abiotic stresses.⁵⁰⁻⁵¹

5-Aminolevulinic acid (ALA) is a novel plant growth regulator synthesized from glutamic acid via enzymatically, where L-glutamic acid is converted to L-glutamyl-tRNA and L-glutamic acid-1-semialdehyde with the combined action of glutamyl-tRNA synthetase and glutamyl-tRNA reductase. Subsequently, L-glutamic acid-1-semialdehyde converted to the ALA with the assistance of enzyme L-glutamic acid-1-semialdehyde aminotransferase.⁵²⁻⁵³ ALA has been reported to mediate tolerance to abiotic stresses such as salinity, drought, heavy metals, and ultraviolet radiation by regulating photosynthetic parameters, ROS metabolism, and soluble nutrient absorption.⁵⁴ However, the effectiveness of different ALA application modes varies significantly and

depends on several factors, including ALA concentration, plant growth stage, plant species, and application timing. Thus, selecting the appropriate ALA concentration and application mode remains an area that requires further exploration.

Horticultural management

Urban garden landscapes are an important product of the urbanization process, providing people with a better and more comfortable living environment. However, addressing the investment issues related to human labour, material resources, and financial resources in the maintenance and management of landscape is crucial for sustaining a high-quality urban living environment and achieving the sustainable development of landscapes. As research on landscape plants deepens, the advantages of PGRs in landscape management are becoming increasingly evident, and their rational application in urban greening projects has emerged as a new technology. PGRs are primarily used to promote root development, increase flowering rates, improve fruit quality, enhance stress resistance, regulate plant morphology, and prolong the freshness of flowers.⁵⁵⁻⁵⁷ Among the diverse soil microbial communities, plant growth-promoting bacteria (PGPB) directly influence crop growth through various mechanisms, playing a vital role in atmospheric nitrogen fixation, mineral nutrient solubilization, and antagonistic actions against pathogens. PGPB have consistently demonstrated their ability to enhance the biological adaptability of economically significant crops.⁵⁸ Notably, certain microorganisms exhibit a combination of multiple traits and show good adaptability to reproduce in environments outside their original isolation sites, thus holding great potential as active compounds in biofertilizer formulations.⁵⁹ The benefits of PGPB for horticulture are multifaceted, making them an effective tool for enhancing horticultural crops. Observations indicate that PGPB can significantly improve plant quality, promote soil health, and facilitate pest and plant pathogen control by reducing reliance on agricultural chemicals.⁶⁰ Recently, researchers discovered a phosphorus-solubilizing bacterium from mountainous regions, *Bacillus thuringiensis* B3, which can serve as a plant growth promoter for lettuce and tomato horticultural crops. The B3 strain exhibits significant phosphorus solubilization capability and plays roles in nitrogen fixation, nutrient mobilization, growth regulation, iron chelation, production of lipases, and antimicrobial compounds. The multifaceted functions of this strain suggest its potential in limiting the proliferation of plant pathogens, contributing to plant health. This study further confirms the diversity of plant growth regulators and underscores that the exploration of these regulators should not be limited to traditional plant endogenous hormones.⁶¹ Recent studies have found that strigolactone not only inhibits the growth of lateral buds in plants, but also that its levels in the shoot correlate inversely with anthesis time and directly with the number of flowers. Additionally, it can promote meristem maturation and flower development by inducing the florigen-encoding gene SINGLE FLOWER TRUSS (SFT), a process that occurs before and after the floral transition.⁶²⁻⁶³ Plant peptides are a new frontier in plant biology, owing to their key regulatory roles in plant growth, development, and stress responses.⁶⁴⁻⁶⁶ Phytosulfokine is a broadly functional plant pentapeptide hormone that can phosphorylate two sites (Serine-334 and Serine-360) on the key enzyme of nitrogen assimilation glutamine synthetase GS2. These two sites regulate plant defense and growth in tomatoes, thereby playing an important role in responding to (hemi)biotrophic pathogens, particularly in the antagonistic regulation of growth and defense.⁶⁷

Cultivation of chinese medicinal herbs

In recent years, the demand for medicinal resources in the traditional Chinese medicine (TCM) pharmaceutical industry has increasingly outstripped supply, placing production pressure on the cultivation of Chinese medicinal herbs. Wild medicinal herbs can no longer meet production needs, necessitating a shift towards artificial cultivation.⁶⁸ The use of PGRs has alleviated some of this pressure, reducing labor requirements for farmers and improving efficiency. Certain PGRs have been shown to significantly impact traits such as plant height, dry weight, and root length in medicinal herbs like *dendrobium officinale*, medicinal lily, and licorice root, promoting the growth of their seedlings and shoots.⁶⁹⁻⁷¹ Additionally, numerous studies have reported that the effective regulation of the synthesis of active components in

medicinal herbs can be achieved through the application of PGRs, enhancing their medicinal value.⁷²⁻⁷³ While the use of PGRs mitigates the pressures associated with cultivating medicinal herbs, it also presents a double-edged sword. Due to the relatively slow advancement of agricultural technology, many farmers lack systematic scientific education on PGRs, resulting in a lack of effective guidance on the rational use of PGRs. The cultivation of medicinal herbs is disorganized in some areas, making it challenging to simultaneously achieve the dual goals of increasing yield and ensuring the stability of active ingredient content in Chinese medicinal herbs cultivation, leading to a phenomenon characterized by "high quantity but low quality".⁷⁴⁻⁷⁵ As the demand for medicinal herbs rises, the transition from wild-harvested to artificially cultivated sources has become an inevitable trend for the future of medicinal herbs. Therefore, it is essential to use PGRs in a scientific and standardized manner, actively promote the improvement of quality management standards in medicinal herb production, and develop new technologies and methods for testing, thereby laying a solid foundation for the healthy development of the TCM industry.

Conservation of Endangered Plants

An ambitious goal of Target of the Global Strategy for Plant Conservation (GSPC) is to save 75% of threatened plant species in ex situ collection, with at least 20% of them available for restoration programs.⁷⁶ However, the 2020 GSPC progress report indicated that over half of endemic threatened species were not conserved ex situ within their countries of origin, implying reduced availability of plant materials for ecological or species restoration. Many of such species originate from the tropics and/or wetlands and do not possess inherited desiccation and chilling tolerance, resulting in seeds that are dormant or low in number.⁷⁷⁻⁷⁸ The combination of low-temperature storage and in vitro techniques offers a valuable new option for the long-term preservation and restoration of these special species.⁷⁹⁻⁸¹ Numerous studies have confirmed that tissue culture techniques can be applied to the conservation of endangered resources, breeding, and the commercial production of clonal seedlings, and the addition of PGRs has become a crucial step for improving the regeneration of plant tissues after low-temperature storage.⁸²⁻⁸⁴ Integrating tissue culture techniques with PGRs can facilitate the rapid and large-scale propagation of endangered plants, providing a viable pathway for their conservation and restoration. By adding PGRs to the culture medium, it is possible to effectively overcome dormancy, suppress browning of callus tissue, enhance regeneration efficiency, accelerate growth rates, promote the formation of roots and shoots, and induce the growth and development of callus tissue.⁸⁵ However, the requirements for growth regulators vary among different species and growth stages, making it a challenge to determine the optimal combinations and concentrations of these regulators.⁸⁶⁻⁸⁹ Future research could focus on developing personalized PGRs tailored to specific endangered species to enhance their efficacy in tissue culture applications. Additionally, integrating knowledge from molecular biology, genomics, and ecology could deepen the understanding of the growth mechanisms of endangered plants, providing a theoretical basis for the application of these regulators. The root-derived CLAVATA3/EMBRYO-SURROUNDING REGION-RELATED 25 (CLE25) peptide moves from the roots to the leaves, where it induces stomatal closure by modulating abscisic acid accumulation and thereby enhances resistance to dehydration stress.⁹⁰

Enhance the efficacy of phytoremediation

Soil contamination caused by potentially toxic elements presents a global challenge to ecological health and food security. Phytoremediation serves as an environmentally friendly technology for remediating heavy metal pollution in soils.⁹¹ It utilizes plants to remediate heavy metals from contaminated soil, offering a cost-effective solution with minimal invasiveness to soil and ecosystems, making it an easily implementable in situ remediation technique.⁹² However, two main factors limit the efficiency of phytoremediation: the bioavailability of heavy metals in the soil and the tolerance of plants to contaminated soils, which is closely related to plant biomass.⁹³

Some studies have shown that PGRs can enhance the immobilization of heavy metal ions in plants and improve their resistance by modulating physiological and biochemical processes, thereby promoting plant growth.⁹⁴ PGRs can reduce oxidative stress caused by heavy metals, significantly alleviate the

absorption of heavy metals by plants, and increase the total chlorophyll concentration within the plants.⁹⁵⁻⁹⁶ In summary, due to their unique advantages in promoting plant growth, enhancing antioxidant capacity, and alleviating heavy metal stress, PGRs have become the preferred option for aiding in the remediation of heavy metal pollution.⁹⁷ Moreover, increasing research indicates that combining PGRs with other techniques can further strengthen the phytoremediation capabilities of contaminated areas. The integration of PGRs with PGPR is particularly beneficial. On one hand, the microorganisms residing in the rhizosphere can facilitate plant development by decomposing toxins and promoting plant growth through chelation, acidification, or phosphate solubilization. At the same time, they can secrete various compounds (such as iron carriers, plant hormones, and metal-binding proteins), which help enhance the plant's resistance. On the other hand, PGRs can enhance plant biomass, mitigate the negative impacts of pollutants, and support plant growth in adverse environments.⁹⁸ Combining PGRs with chelating agents can reduce the mobility of heavy metals in the soil while simultaneously increasing chlorophyll content and antioxidant enzyme activity in plants, thereby enhancing plant stress resistance and improving phytoremediation performance.⁹⁹ Based on the findings of research that integrates PGRs with other techniques to enhance phytoremediation, future studies could explore various combinations of PGRs with biodegradable chelating agents or other technologies tailored to the specific contaminated soils in different regions. This approach aims to enrich the selection and application scope of soil pollution remediation technologies.

Overall, the application of PGRs is extensive. With the increasing global demand for food and medicinal materials, utilizing PGRs to enhance the productivity and quality of crops will become an important research direction. Concurrently, novel regulators will support sustainable ecological protection and promote environmentally friendly remediation models characterized by low energy consumption, minimal pollution, and high efficiency. In the future, with advancements in technology, the application of PGRs will become more precise, integrating genetic engineering, biotechnology, and artificial intelligence to enable personalized adjustments based on the plant's growth stages and environmental conditions. This approach will facilitate the development of new plant growth regulators that are environmentally friendly, efficient, and intelligent, thereby contributing to the advancement of sustainable agricultural practices and ecological conservation efforts.

GROWTH REGULATION METHODS MEDIATED BY PLANT REGULATORS

Regulatory effects of hormones synthesized via a single pathway

Plant hormones are typically present in quantities that directly influence plant growth. Traditional plant hormones are extracted from plant sources (commonly from coconut, tomato, sesame, rice, mushrooms, etc.) using methods such as solvent extraction, water extraction, ultrasonic extraction, solid-phase extraction, and enzymatic hydrolysis, these extracts can be directly applied at specific stages of a plant's life cycle to regulate its growth (Figure 3A).¹⁰⁰⁻¹⁰² In recent years, various biological and non-biological stimulants have been discovered that can stimulate the synthesis of hormones in plants through physical or chemical means, thereby indirectly affecting plant growth. These stimulants can be categorized into biostimulants and abiotic stimulants based on the principles of their induction.

Biostimulants generally include: (1) Microbial extracts, which serve as active elicitors, have been widely used to enrich valuable bioactive compounds in vitro by inducing plant resistance responses.¹⁰³ For example, the Nod factors secreted by Rhizobium can specifically induce cytokinin synthesis, while the ACC deaminase produced by Pseudomonas can effectively reduce ethylene synthesis inhibition (Figure 3B).¹⁰⁴⁻¹⁰⁵ (2) Chitosan, a valuable deacetylated derivative of chitin, can enhance plant defense responses against biotic or abiotic stresses (Figure 3C).¹⁰⁶ Chitosan primarily regulates hormone synthesis by activating plant immune signaling pathways. Low-dose chitosan can be recognized by plants as an elicitor, activating the expression of hormone synthesis-related genes through the MAPK signaling cascade.¹⁰⁷⁻¹⁰⁸ (3) Algal extracts, due to their rich bioactive components, have become ideal complex hormone inducers (Figure 3D).¹⁰⁹ Active substances such as oligosaccharides, betaine, and polyunsaturated fatty acids found in seaweed can collaboratively regulate plant hormone synthesis through multiple mechanisms, activating plant defense responses.¹¹⁰ Numerous studies

have confirmed that seaweed extracts can be used as bioregulators to improve crop yield and enhance water and nutrient uptake, or to alleviate various abiotic and biotic stresses experienced by plants, including salinity, drought, temperature, and pathogen attacks.¹¹¹⁻¹¹² Currently, algal extracts hold a significant position in the global biostimulant market, with demonstrated efficacy particularly notable in enhancing crop resilience and improving quality.¹¹³

Abiotic stimulants: (1) Nanoparticles are a novel class of abiotic plant inducers, including nano-silicon (nano-Si), zinc oxide nanoparticles (ZnO NP), iron oxide nanoparticles (Fe NPs), and silver nanoparticles (Ag NP). These nanoparticles can influence hormone synthesis by regulating signaling pathways and enhancing nutrient absorption efficiency, thereby promoting plant growth and increasing stress resilience (Figure 3E).¹¹⁴⁻¹¹⁵ (2) Melatonin (N-acetyl-5-methoxytryptamine) serves as a multifunctional plant hormone regulator, participating not only in the regulation of circadian rhythms but also exerting its effects by modulating various elements related to the redox network or interfering with the activity of other plant hormones, enhancing plant tolerance to abiotic stresses (Figure 3F).¹¹⁶⁻¹¹⁸ These abiotic elicitors demonstrate promising applications in modern sustainable agriculture due to their efficiency and environmentally friendly characteristics.

Regulatory effects of hormones synthesized via multiple pathways

Although single plant growth regulators can produce good effects in certain specific applications, their shortcomings in terms of serviceable range, persistence, and environmental impact restrict their widespread use in agriculture. Consequently, there is a growing focus on composite PGRs in both research and practice. These composite agents combine different types of PGRs with the aim of overcoming the shortcomings of individual regulators and achieving more efficient plant growth regulation.

Recent studies have shown that nanoparticles (NPs) can effectively mitigate abiotic stress through synergistic interactions with PGRs. The cooperative interaction between NPs and PGRs promotes plant tolerance, enhances photosynthetic characteristics, and improves seed germination rates, as well as stimulating physiological and biochemical functions that facilitate plant growth and development.¹¹⁹⁻¹²³ Specifically, NPs enhance the plant's antioxidant defense by interacting with stress indicators (H_2O_2 , O_2^- , MDA, etc.), which can help stabilize cell membranes and protect the photosynthetic system from oxidative damage caused by abiotic stresses, ultimately resulting in an increase in plant growth.¹²⁴⁻¹²⁵ The combination of seaweed extracts and humic acid has been found to improve the growth parameters of leafy vegetables, increasing total ascorbic acid, phenolic content, and antioxidant capacity, which more effectively reduces post-harvest crop loss compared to their individual application.¹²⁶ The combination of seaweed extracts with chitosan can enhance disease resistance by upregulating the expression of genes involved in defense mechanisms, such as salicylic acid (SA) and jasmonic acid.¹²⁷ Research has confirmed that using biodegradable chelators in conjunction with PGRs can enrich microorganisms with strong heavy metal stress tolerance, further promoting plant growth under Cd stress.¹²⁸ The combination of SA and spermidine (Spd) can help plants maintain osmotic levels (proline, total soluble sugars, and total carbohydrate) under dual stress conditions of drought and chromium (Cr), adjusting Cr transport between roots and shoots, and protecting antioxidant enzyme activity to maintain the cellular redox state and enhance plant tolerance to Cr toxicity.¹²⁹ Co-application of the salt-tolerant bacterium *A. xylosoxidans* and methyl jasmonate (MeJA) in buckwheat plants (*Fagopyrum esculentum* L.) under salt stress has proven to be more effective than individual treatments, resulting in maximum root biomass, chlorophyll, and carotenoid content in the combined application group, along with stronger defense enzyme activity and higher proline levels contributing to salt stress mitigation.¹³⁰ The combined application of PGRs with mineral elements is beneficial for the content of photosynthetic pigments, antioxidant enzyme activity, and translocation in grapevine leaves.¹³¹

In summary, the effects of different growth regulators vary due to differences in effective components, action sites, application timing, and mechanisms. One of the key principles for the combined use of agents is to achieve a synergistic effect. Composite plant growth regulators not only help promote

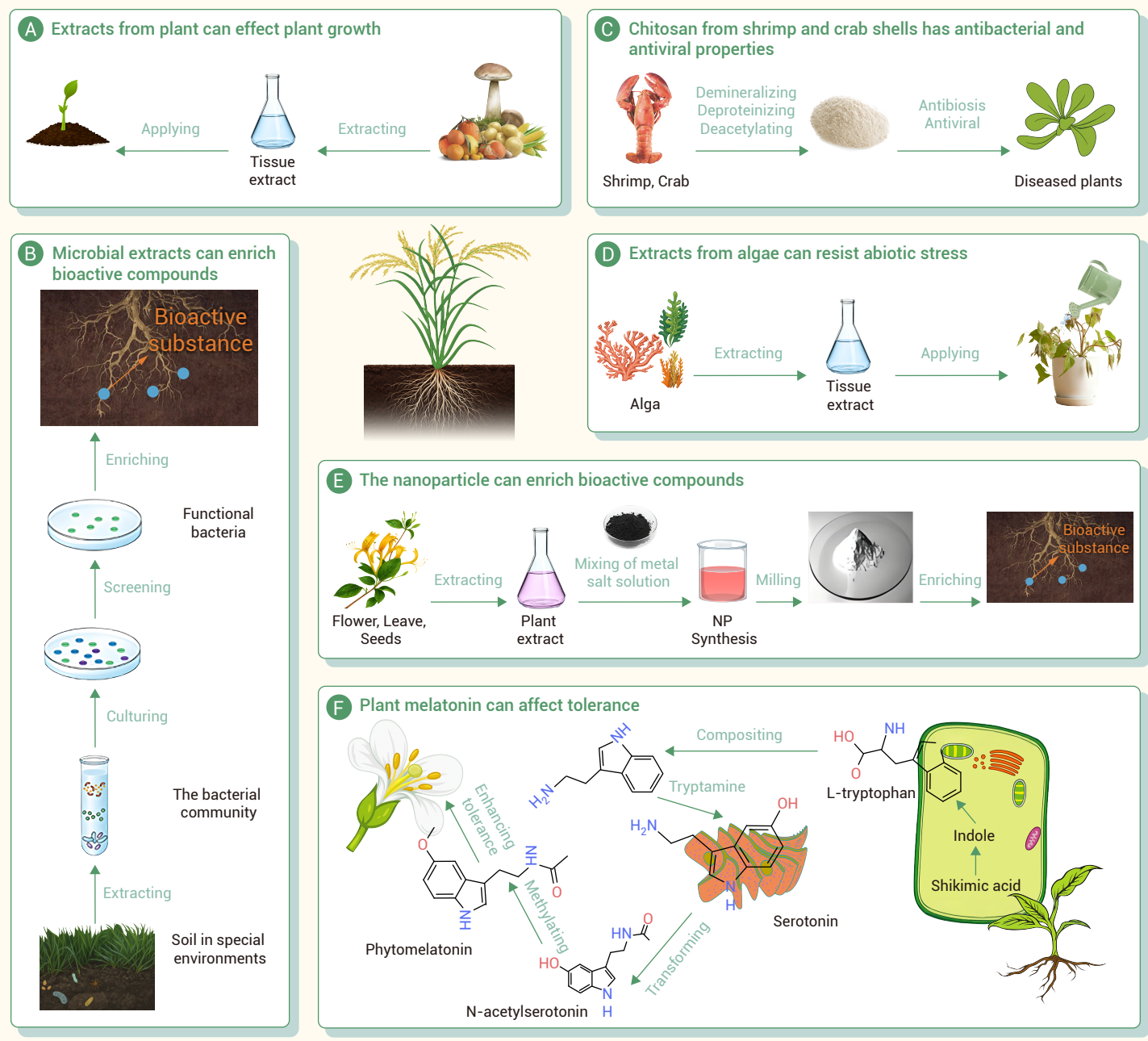


Figure 3. Classification and Extraction of plant growth regulators.

crop growth, enhance crop stress resistance, and delay crop senescence, but they also have practical significance for reducing pesticide usage and minimizing environmental pollution from pesticides.

CHALLENGE

Residual problems caused by the abuse of PGR

PGRs play a crucial role in regulating and controlling various stages of plant growth and development. The use of PGRs can yield significant economic benefits; however, the threats to human health and the ecological environment caused by excessive use and misuse of PGRs cannot be overlooked (Figure 4).

Regarding threats to human health, common toxic reactions associated with PGRs include several aspects: in terms of reproductive toxicity, they can affect individual hormone levels, promote apoptosis of germ cells, and inhibit sperm motility; concerning hepatotoxicity, they can interfere with the activity of serum enzymes such as ALT, AST, and LDH in the liver, causing damage to liver cells and altering the normal morphology of liver tissue. Additionally, PGRs exhibit immunotoxicity, neurotoxicity, teratogenicity, and carcinogenicity.

¹³²⁻¹³³ The misuse and abuse of PGRs in the cultivation of medicinal ingredients not only pose health risks but also significantly affect the efficacy of these medicinal materials.¹³⁴

Regarding ecological damage, over 70% of PGRs enter the soil, with less than 30% remaining on the plant surface.¹³³⁻¹³⁶ Additionally, most PGRs exhibit high water solubility, leading to their lateral and vertical migration in saturated soils. These substances can undergo adsorption, desorption, and degradation processes in the unsaturated zone. If they are not completely removed before reaching groundwater, they pose a threat to groundwater safety.¹³⁷⁻¹³⁸ The environmental behavior of PGRs in soil is complex. Chemicals applied to plant leaves inevitably leach into the soil and are difficult to decompose. Residues that accumulate in the soil can alter pH levels and the solubility of soil components, thereby affecting the growth of sensitive crops. Notably, the environmental behavior of PGRs is multifaceted, and certain degradation intermediates of PGRs may exhibit higher toxicity. For instance, primary hydrolysis products of gibberellins, such as isomeric gibberellins and byproducts like gibberellic acid and hydroxyl gibberellic acid, show greater toxicity than gibberellin itself.¹³⁷ Novel PGRs derived from pyridine nitrogen

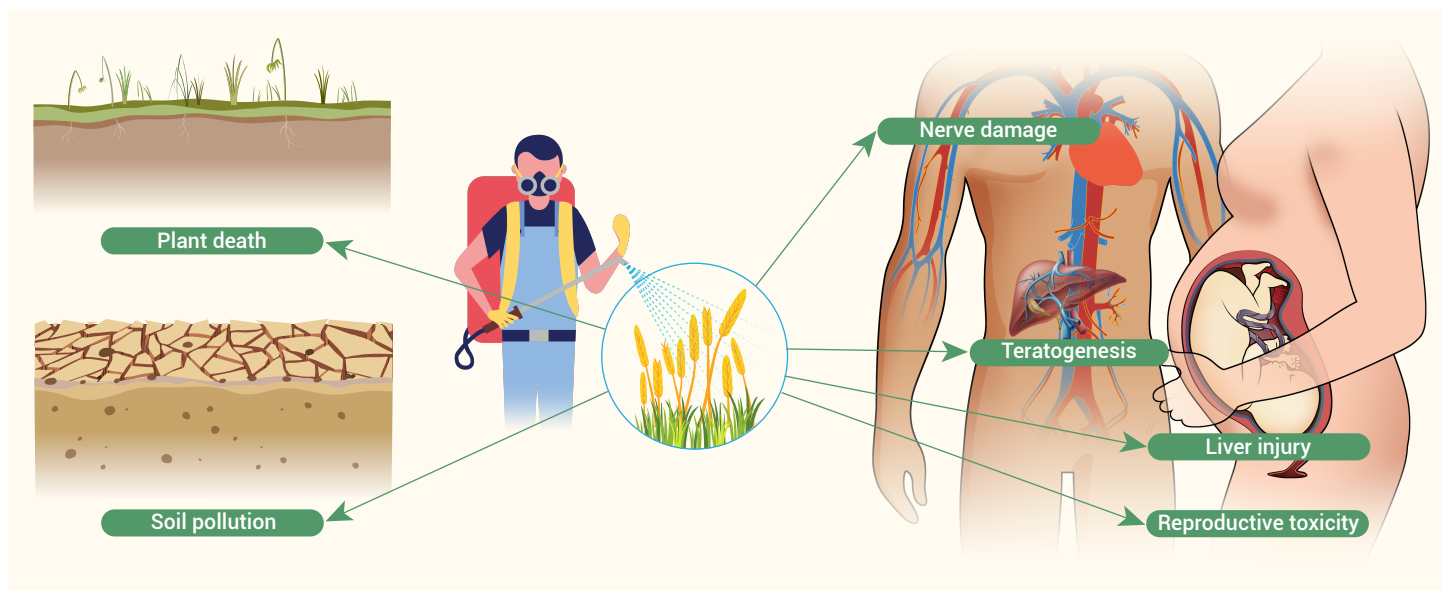


Figure 4. Safety issues caused by residues of plant growth regulators.

oxides form complexes with metal salts and organic acids, exhibiting moderate toxicity (LC_{50} : $2.76\text{--}13.92\text{ mg}\cdot\text{L}^{-1}$).¹³⁹

Therefore, during the production and application of PGRs, it is essential to fully consider their toxic effects in order to achieve the maximum regulatory effect with the safest dosage while minimizing residue levels. Establishing comprehensive residue limit standards for plant growth regulators in crops, medicinal herbs, and other applications poses an important challenge in reducing the hazards associated with PGR residues.

Reveal the mechanism of action of PGR

Climate fluctuations and environmental pollution have negatively impacted crop production and plant protection.¹⁴⁰ The application of PGRs to plants can regulate physiological processes under adverse conditions, serving as a relatively efficient method to help plants combat various external stresses. However, there is a lack of clear understanding regarding the mechanisms of action of PGRs. Different types of PGRs exhibit significant variations in their modes of action and mechanisms. The related research on the regulatory effects of PGRs in plants appears to be primarily focused on physiological effects rather than molecular mechanisms.

An increasing number of studies indicate that plant hormone signaling and epigenetic mechanisms represent different strategies employed by plants to achieve common outcomes, such as fundamental development and environmental plasticity.¹⁴¹ There are multi-layered interactions between plant hormone signaling and epigenetic mechanisms. The plant hormone signaling and epigenetic mechanisms jointly regulate common target genes or physiological traits downstream in their respective pathways.¹⁴² Certain secondary metabolites, such as flavonoids, alkaloids, and terpenoids, which provide protective roles against biotic and abiotic stresses, are biosynthesized in response to exogenous PGRs.¹⁴³⁻¹⁴⁴ PGRs can regulate the accumulation of flavonoids by downregulating the relative expression levels of key genes involved in flavonoid biosynthesis and inhibiting enzyme activity, or they may indirectly suppress the biosynthesis of endogenous plant hormones to promote flavonoid accumulation.¹⁴⁵⁻¹⁴⁸ Studies have found that many plant hormones act as inducers of protein-protein interactions (PPIs) between their receptors and co-receptors; compounds that can induce or disrupt these interactions represent potential agonists or antagonists. Phenotypic, biochemical, pharmacological, and transcriptomic analyses of different hormone mutants aid in elucidating the downstream components and transduction networks involved in hormone signaling, as well as clarifying similar signaling patterns among hormones.¹⁴⁹⁻¹⁵¹

In conclusion, the elucidation of the mechanisms of action of PGRs can be achieved through various technical approaches, including molecular biology techniques (such as quantitative real-time PCR and RNA sequencing to

analyze changes in gene expression, and transgenic technologies to study the functions of specific genes),¹⁵² plant physiological assays (to assess growth rates and changes in hormone levels),¹⁵³⁻¹⁵⁴ biochemical analysis techniques (to measure relevant enzyme activities and utilize metabolomics to study changes in metabolites),¹⁵⁵⁻¹⁵⁶ and systems biology (to construct gene regulatory networks and signaling pathway models, and apply bioinformatics to analyze gene and protein interactions).¹⁵⁷⁻¹⁵⁸ The integration of these methods helps to understand the overall molecular mechanisms and provides a comprehensive understanding of the functions of PGRs in plant growth and development, thereby offering a theoretical basis and practical guidance for the development of novel plant growth regulators (Figure 5).

Development of composite PGR formulations using machine algorithms

Secondary metabolites are important components of plant defense mechanisms, and their protective functions in resisting biotic and abiotic stresses have been well established. Therefore, using different types of PGRs to activate these defense mechanisms is an effective strategy for enhancing the in vitro production of these defense components. Numerous studies have demonstrated that different types of PGRs can lead to significant variations in the accumulation of secondary metabolites within specific plant genomes. Thus, it is essential to identify the types or combinations of plant growth regulators that increase the accumulation of beneficial chemical compounds. However, determining the optimal type, concentration, and combination of PGRs is a complex task.

Researchers have employed various nonlinear machine learning algorithms, including random forest (RF), support vector machines (SVM), and artificial neural network (ANN), to analyze different multifactorial in vitro experiments.¹⁵⁹⁻¹⁶¹ Among these computational methods, response surface methodology (RSM) combined with ANN has shown significant potential in optimizing in vitro culture performance and enhancing the production of various bioactive compounds.¹⁶² Kaur et al. (2020) utilized RSM and ANN to model and optimize the induction of salicylic acid and chitosan to synthesize bitter compounds, secoiridoids, and xanthone glycosides in the shoot cultures of *C. avellana*. Based on the optimization results, the authors found that under different combinations of salicylic acid concentrations (1-20 mM) and chitosan (1-20 mg/L), they could obtain 0.170-0.435% amarogentin, 1.020-4.987% gentiopicoside, and up to 2.550-4.357% mangiferin. Furthermore, statistical results based on root mean square error (RMSE), absolute average deviation (AAD), and regression coefficient (r^2) indicated that ANN was more precise than RSM in optimizing inducers to promote the production of secoiridoids and xanthone glycosides.¹⁶³ In another study, Salehi et al. (2020a) utilized a multilayer perceptron-genetic algorithm (MLP-GA) to investigate the effects of fungal inducers (cell extracts and culture filtrates from

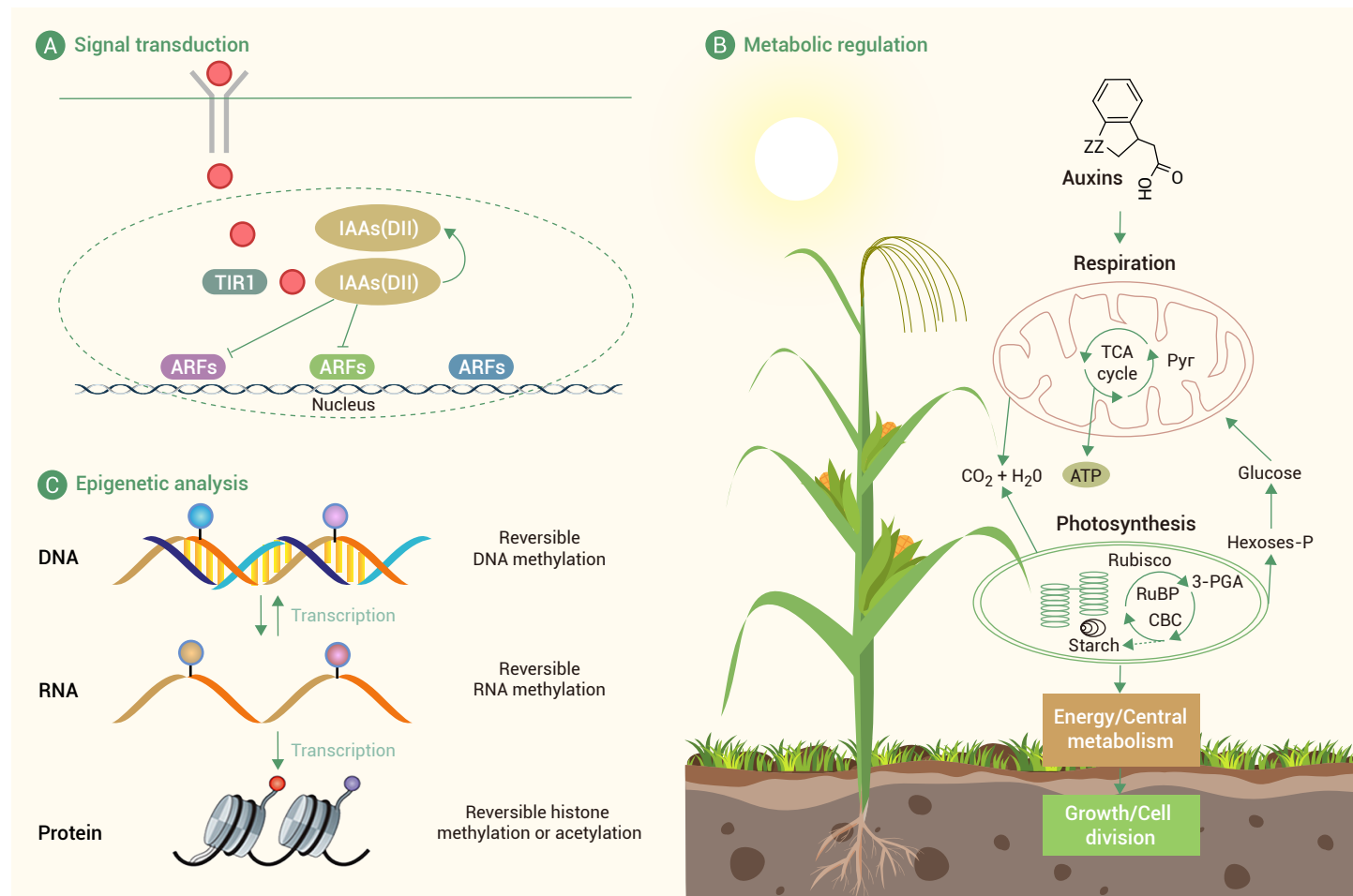


Figure 5. Analysis of the mechanism of action of PGRs.

the HEF17 fungal strain isolated from *C. avellana*) by using cell extract concentration, culture filtrate concentration, inducer addition time, and harvest time of cell suspensions as model inputs. The dry weight of paclitaxel and the intracellular, extracellular, and total yields were used as outputs, identifying the optimal conditions for the biosynthesis of paclitaxel in *C. avellana* cell suspensions. The authors noted that the developed MLP-GA model was more precise than traditional regression models, demonstrating its potential application value in predicting the fungal inducer-assisted biosynthesis of paclitaxel in *C. avellana* cell suspensions (Figure 6).¹⁶⁴

These results demonstrate the power of machine learning algorithms in modeling and optimizing experimental setups. By utilizing these robust computational methods, researchers are able to manage a wide range of factors, including medium optimization, precursors, biotic and abiotic inducers, physical stress, and tolerance-enhancing additives, as well as their interactions in different culture systems, to facilitate the large-scale in vitro production of valuable bioactive compounds.

As cutting-edge technologies for detecting critical steps and conditions in specific protocols, machine learning algorithms can manage and process large volumes of data while considering various factors such as culture systems, precursor feed, induction, and medium parameters. Therefore, in the future, there is potential for increased application of artificial intelligence systems in empirical experiments to manage the interactions of different tools available for enhancing the in vitro production of secondary metabolites.

CONCLUSIONS AND RECOMMENDATIONS

The emergence of plant growth regulators (PGRs) marks a significant turning point in botanical research, enhancing our understanding of plant growth and development. PGRs have helped overcome barriers previously considered insurmountable in the plant growth process, mainly reflected in improving plants' resistance to environmental stresses, increasing crop yield and

quality, facilitating precise growth regulation, advancing agricultural technology, and addressing climate change. This has made PGRs an important area of research over the years. However, as application scenarios become increasingly complex, the development and management of PGRs face substantial challenges. In this review, we focus on the research advancements and future prospects of PGRs. First, we discuss the types of PGRs that influence processes such as cell division, elongation, flowering, and fruit development, including plant growth promoters, plant growth inhibitors, and plant growth retardants, which provide a basis for understanding the mechanisms of PGRs. Next, we emphasize the multifaceted impacts of PGRs, highlighting their practicality in crop yield enhancement, horticultural management, and conservation of endangered plants. Based on the singular and composite regulatory approaches of PGRs, we summarize the current status of PGR development. Finally, we outline the challenges PGRs face in future development, including the necessity of improving application efficiency while ensuring agricultural sustainability and addressing potential negative impacts of residues. We explore how cutting-edge technologies such as nanotechnology, genetic engineering, and bioinformatics can offer new possibilities for the development and mechanistic elucidation of novel PGRs. Additionally, we discuss how machine learning can optimize PGR formulations and application timing to maximize their effectiveness while minimizing environmental impact.

Based on the recommendations from this review, several points should be addressed:

First, it is essential to further improve the management policies for plant growth regulators (PGRs), particularly by establishing usage standards for the production of medicinal herbs. Research on the movement rates and residue behavior of PGRs in soil and plant tissues is limited, leading to insufficient understanding of their chronic and ecological toxicity. Establishing quality standards for PGRs is necessary for the scientific regulation of medicinal

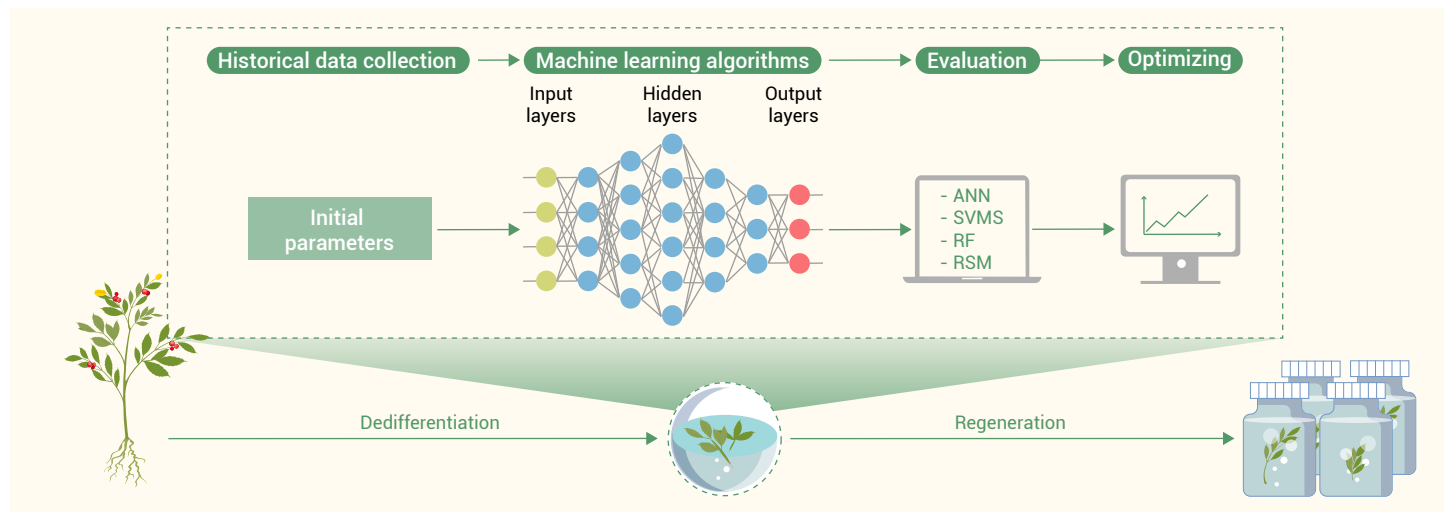


Figure 6. Intelligent optimization of the formulation process for novel PGRs.

herb production.

Second, there should be a push to accelerate the replacement of chemical fertilizers and pesticides with biological PGRs, such as seaweed extracts and mineral bio-fertilizers. Education and encouragement for farmers to use these seaweed-based biostimulants in their fields, instead of conventional chemical fertilizers and pesticides, is crucial.

Next, further screening or development of growth promoters suitable for terrestrial or aquatic plants is needed, integrating PGRs into ecological restoration efforts to address existing environmental issues. Phytoremediation technologies still face challenges due to difficulties in plant survival, establishment, and proliferation. Applying PGRs to aquatic plants can significantly enhance their establishment and proliferation, thereby amplifying their role in water body remediation and promoting further application of ecological restoration technologies.

Finally, incorporating artificial intelligence into the research and application processes of PGRs can improve production efficiency. Through technologies such as machine learning, rational formulation of PGRs can be achieved, and the optimal combinations can be identified, facilitating faster development and enhanced effectiveness. The application of plant growth regulators will increasingly become more intelligent, utilizing sensors and data analysis technologies to achieve real-time monitoring of plant conditions and adjust application strategies accordingly.

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FUNDING AND ACKNOWLEDGMENTS

This work was supported by National Natural Science Foundation of China (No. 31830013;32201384; 42307336); National Natural Science Foundation of Hubei Province Youth A (JCZRJQ20250047); Key Research and Development Program of Hubei Province, China (2022BCA066; 2024BCB062); China Postdoctoral Sciences Foundation (2024M763481); Key Research and Development Program of Hubei Province, China (2024BCB062); Wuhan Science and Technology Plan Project (2023020402010623); The project of cross-disciplinary research team of state key laboratory of breeding biotechnology and sustainable aquaculture (2024BBSA09). We thank Ms. Liping Zhang for the experimental help. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

AUTHOR CONTRIBUTIONS

Yunli Liu, Yuwen Hu, Tianlun Han, Xiaopei Du, Guoliang Bai, and Weixiang Xu wrote and edited the manuscript. Ming Kong, Hang Yang, Yadong Tang, Zhenbin Wu, Qiaohong Zhou, and Yi Zhang supervised and revised the manuscript. All authors contributed to the manuscript and approved the final version.

DECLARATION OF INTERESTS

The authors declare no competing interests.

DATA AND CODE AVAILABILITY

Data are available from the corresponding author upon reasonable request.