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Plant Biostimulant as an Environmentally Friendly Alternative to Modern Agriculture

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ABSTRACT: Ensuring the safety of crop production presents a significant challenge to humanity. Pesticides and fertilizers are commonly used to eliminate external interference and provide nutrients, enabling crops to sustain growth and defense. However, the addition of chemical substances does not meet the environmental standards required for agricultural production. Recently, natural sources such as biostimulants have been found to help plants with growth and defense. The development of biostimulants provides new solutions for agricultural product safety and has become a widely utilized tool in agricultural. The review summarizes the classification of biostimulants, including humic-based biostimulant, protein-based biostimulant, oligosaccharide-based biostimulant, metabolites-based biostimulants, inorganic substance, and microbial inoculant. This review attempts to summarize suitable alternative technology that can address the problems and analyze the current state of biostimulants, summarizes the research mechanisms, and anticipates future technological developments and market trends, which provides comprehensive information for researchers to develop biostimulants.

KEYWORDS: *biostimulants, plant growth and defense, agricultural produce, pesticides and fertilizers, plant immunity, modern agriculture*

1. INTRODUCTION

The global demand for crops is increasing year by year, making it imperative to ensure the quality of agricultural products.[1−3] Plants require various nutrients from the surrounding environment and encounter numerous biological and abiotic stresses during their growth.[4] Historically, pesticides and fertilizers have been wildly used to provide nutrients for plant growth and eliminate external biological factors that hinder plant development.[2,5−7] However, the use of these chemicals has resulted in environmental pollution, and their efficacy is increasingly failing to meeting the requirements of modern agriculture.[8,9] Recently, natural substances have been integrated into fertilizer and pesticide products as an alternative to tackle the issues associated with conventional counterparts.[10−12] Biostimulant was defined as a single substance or a mixture that improve nutritional efficiency, abiotic stress, and crop quality.[13] In general, plant biostimulants also refer to a commercial product that contains a combination of these substances and/or microorganisms.[14] Although the definition of biostimulant lacks full standardization, the concept of "biological stimulation" was initially proposed by Filatov of the Soviet Union in 1933.[15,16] It suggests that when plants are exposed to adverse but nonlethal conditions, they undergo biochemical recombination, resulting in the formation of nonspecific biological stimuli that stimulate a biological response.[17,18] Herve was a pioneer in presenting a comprehensive methodology for the production of biostimulants. He emphasized the importance of adopting a systematic approach that integrates chemical synthesis, biochemistry, and biotechnology. According to Herve, biostimulants should be designed to operate effectively at low dosages while remaining ecologically friendly.[19] Du Jardin conducted the first comprehensive analysis of plant biostimulants, focusing on their physiological and biochemical functions, modes of action, and sources.[13] This analysis and classification significantly influenced the subsequent development of legislation and regulation in the European Union.[20] The inaugural World Congress on Biostimulant Agriculture, held in Strasbourg in November 2012, marked a crucial milestone in the academic acceptance of biostimulants.[21] The initial subclasses proposed by the Biostimulation Consortium include antioxidants, amino acid materials, biomolecule complexes, enzyme extracts, fulvic acid materials, humic acid materials, microbial bactericides, microbial soil amendments, mycorrhizal fungi, plant growth-promoting rhizobacteria (PGPRs), plant hormones, and seaweed extract materials.

When plants are infected by various pathogens, they allocate their energy for vegetative growth toward defense mechanisms, resulting in a decline in growth quality. While many pesticides can eradicate pathogens or impede their spread in plants, their environmentally unfriendly nature makes them unsustainable solutions. In 2014, American scientists pointed out that biological control microorganisms and plant growth-promoting microorganisms to enhance plant growth and development, induce resistance in plant systems, and improve plant tolerance

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to biological and abiotic stress.[22] In a way, biostimulants were first defined as nonbiological stimulants, distinguishing them from other commonly used substances in plants and crops, such as fertilizers and pesticides. The application of biological stimulants has evolved from initially promoting growth and regulating development and quality characteristics to enhancing the tolerance of environmental stress. More recently, some biological stimulants have been found to exhibit plant immune characteristics, and pretreatment with these stimulants can enhance plant immunity, leading to the development of "immune inducer". Many plant pathologists have developed natural substance extracts due to their unique ability to pretreat plants and stimulate plant resistance. These extracts are increasingly used in agriculture as inducers of plant defense, and researchers are researching their mechanism.

In recent years, with advancements in science and technology, an increasing number of biostimulants have been developed and applied to agriculture on a larger scale. More and more attention has been focused on biostimulants for promoting plant growth and enhancing plants' adaptive defense against the environment. In addition, there are various types of biostimulants, and their modes of action are complex and diverse. Therefore, it is crucial to have a more comprehensive understanding of the different types of biostimulants. While some articles and reviews provide in-depth studies and summaries of biostimulants, there is a need for more focus on unilaterally describing the effects of biostimulants on plant growth or plant defenses against biological or abiotic stresses. Our review summarizes the different types of biostimulants, presents an updated classification, and provides a summary of the latest research findings. Furthermore, we summarize the mechanisms of action, development, and synthesis of biostimulants. We hope that our review will assist researchers in studying the mechanisms of biostimulants and their application in crops.

2. CLASSIFICATION OF THE BIOSTIMULANTS

For the moment, the classification of biostimulants is still in a relatively vague stage. According to different sources, this review classifies biostimulants into humicin-based biostimulants, protein-based biostimulants, oligosaccharide-based biostimulants, metabolite-based biostimulantss, inorganic substance and organic compounds, and microbial inoculant. We present the sources of different types of biostimulants and their examples in Table 1.

2.1. Humic Biostimulants. Humic acid (HS) is a crucial component of organic matter. It is the result of the decomposition of plant, animal, and microbial residues as well as the result of the metabolic activities of soil microorganisms using these substrates. It is also the substance formed in the process of soil, animal feces, low-rank coal (such as peat, lignite, weathered coal etc.), and agricultural products and waste treatment.[20] It was originally classified based on its molecular weight and solubility into humic, fulvic acid, and humic acid. As a biostimulant, HS can promote plant growth by promoting the development of plant roots. At the same time, it can improve the plant rhizosphere environment, improve soil structure and fertility, accelerate plant metabolism, improve plant stress resistance, and reduce the occurrence of diseases and pests. Aguirre et al.[75] found that humus substances could improve the germination rate of tomato, wheat, rice, corn, *Arabidopsis*, and other seeds. HS has been widely used in agricultural production due to its unique

Table 1. Characteristics of Biostimulant Classes

classification	sources	example
humic-based biostimulants	The substance formed in the process of soil, animal feces, low-rank coal (peat, lignite, weathered coal, etc.) and agricultural products and waste treatment[23]	humin,[24] humic acid,[25] fulvic acid[26]
protein-based biostimulants	plant residues (seeds, crop stalks), animal tissues (collagen, epithelial tissue), amino acids, peptides, protein mixtures, and nitrogen-containing compounds like betaine, polyamines, and nonprotein amino acids[27,28]	harpin,[29] flagelin,[30] Nep1-like protein,[31] EF-Tu,[32] alfalfa plant hydrolysate,[33] superoxide dismutase,[34] siderophore,[35] necrosis-inducing protein,[36] Gr-VAP1,[37] coatprotein,[38] rapid alkalinization factor,[39] pipecolic acid,[40] γ-aminobutyric acid,[41] carob germ hydrolysate[42]
oligosaccharide-based biostimulants	derived from various sources such as the cell walls of pathogenic microorganisms, plants or animal shells[43]	alginate oligosaccharides,[44,45] chitin,[46] heptaglucoside,[47] peptidoglycan,[48] exopolysaccharides,[49] D-trehalose anhydrous,[50] laminarin,[51] xyloglucan[47]
metabolites-based biostimulants	plant secondary metabolites and soluble microbial products (SMSs), such as lipid substance[52]	rutin,[53] quercetin,[54] isoquercetin,[55] ZNC,[56] 2′-Dg,[57] guanine,[58] ATP,[59,60] lipopolysaccharides,[61] ergosterol,[62] eicosapentaenoic acid,[63] arachidonic acid,[64] cerebroside[65]
inorganic substances and organic compounds	nature or remodel	copper ion,[66,67] SiO_2,[68] ozone,[69,70] sulfite[71]
microbial inoculants	natural beneficial bacteria	AMF,[72] *Bacillus subtilis*,[73] trichoderma[74]

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physiological functions, wide availability, low production cost, and diverse application methods. HS can enhance plant resistance to a variety of biological stresses. Horinouchi et al.[76] demonstrated that HS can regulate plant physiological metabolism and stress by affecting the transmission pathway of plant signals. Trevisan et al.[77] found that HS can promote the growth of rice seedlings under water stress and enhance the efficiency of photosynthesis. The contents of chlorophyll, carotenoids, soluble protein, and soluble sugar in rice seedlings increased significantly after being treated with HS.

Humus substances play an important role in maintaining soil fertility. The biological promotion effect of HS is to improve root nutrition through different mechanisms. High molecular weight HS have been shown to enhance the activity of this key metabolic enzyme in hydroponically grown maize seedlings, indicating the regulatory effect of HS on stress response.[78] In addition, HS can improve soil structure and promote the formation of soil aggregate structure, adjust soil pH value, fertilizer, gas, heat, and other conditions.[79,80] It can also improve soil exchange capacity, achieve acid−base balance, improve soil water and fertilizer retention ability, and promote soil microbial activities.[81−83] HS can decrease the strength of stomatal opening in plant leaves, reducing leaf transpiration, and consequently lowering water consumption.[84] HS is mostly amphoteric colloid, large surface activity, has an inhibitory effect on fungi, can enhance the cold pit of crops, can easily be adsorbed by cell membranes, change the permeability of cell membranes, promote the absorption of inorganic nutrients, and reduce pests and diseases.[85,86] In addition, agricultural byproducts do not decay in the soil or through composting, but through chemical processes that can control decomposition and oxidation, resulting in the formation of "humic-like substances" that have been proposed as alternatives to natural HS.[87]

2.2. Protein-Based Biostimulant. Protein biostimulants, such as protein hydrolysates (PH) and amino acids, are derived from various sources, including plant residues (seeds, crop stalks), animal tissues (collagen, epithelial tissue), amino acids, peptides, protein mixtures, and nitrogen-containing compounds like betaine, polyamines, and nonprotein amino acids.[13,88,89] These substances can be obtained through enzymatic, chemical, or hot water hydrolysis of these sources as well as from industrial and agricultural byproducts. The main components of plant-based protein hydrolysate and animal-based protein hydrolysate were found to be significantly different. Glutamate seems to be the component of animal protein hydrolysates. Most vegetable protein hydrolysates do not contain histidine or ornithine.[90] However, the composition of the hydrolysate is closely related to the processing technology and the cultural conditions. Amino acids, peptides, and their derivatives are the main components of protein hydrolysates. Over the past 20 years, proteolytically active peptides have been identified as molecular signals for plant growth and defense, for example, soybean-derived PHs,[91] systemins,[92] phytosulfokines,[93,94] and clavata3.[95] Protein hydrolysates and amino acid derivatives have been shown to promote organic matter accumulation by significantly increasing chlorophyll content and carbon uptake, thereby enhancing plant physiology.[96,97] When absorbed and transported by plant roots, the amino acids and small peptides derived from protein hydrolysis regulate plant metabolism, physiological and biochemical reactions, promote seed germination and root development, enhance nutrient absorption, and improve plant stress resistance.[98,99] The direct impacts include regulating nitrogen uptake and assimilation through the modulation of nitrogen assimilation-related enzymes and their structural genes, as well as through signaling pathways involved in nitrogen acquisition in the root system.[100−102] Protein hydrolysates also contribute to metabolic crosstalk between carbon and nitrogen by regulating enzymes in the TCA cycle.[103] Additionally, the hormone activity is reported to be influenced by complex protein and tissue hydrolysates. In agricultural production, the indirect effects of applying protein hydrolysates to plants and soil are also significant for plant nutrition and growth. Protein hydrolysates can increase microbial biomass and activity, enhance soil respiration, and improve the overall soil fertility. Specific amino acids and peptides are believed to enhance the utilization of nutrients and root absorption through chelating and complexing activities.

Numerous protein-based biostimulants have been identified for their ability to stimulate plant resistance. For example, the hripin protein, which was discovered early and has been widely applied, was isolated as an allergenic active protein from pear fire blight (*Erwinia amylovora*). Another protein-based biostimulant, known as the hypersensitive protein (harpin), reduced the resistance to the fire blight bacterial pathogen *Erwinia amylovora*.[104] Harpin is a glycine-rich and heat-stable protein that activates plant defense resistance against a broad range of pathogens. Harpins have been classified into four major groups (Hpa1, HrpN, HrpW1, and HrpZ1) based on domain structures and protein similarity.[105] In *Arabidopsis thaliana*, Hpal XOO derived from bacterial blight in rice induces the production of H_2O_2 and enhances pathogen resistance.[76] Subsequent classified for promoting CO_2 transport in mesophyll cells, which enhances photosynthesis and the growth of leaves. It was later confirmed that ethylene and gibberellin coregulate the induction of Hpa1, promoting plant growth and related physiological and molecular reactions.[106,107] Hpa1 not only has an effect on disease resistance but also plays a defensive role in insect resistance.[108] These findings emphasize the diverse functions and applications of protein biostimulants in plant physiology, growth, stress response, and defense mechanisms.

The Nep1-like protein (NLP) family is a well-known group of protein-based biostimulants that share similarities with Harpin proteins in their ability to regulate plant hormone pathways. NLPs are found in bacteria, fungi, and oomycetes, particularly in plant pathogens. The Nep1 protein was initially isolated and purified from *Fusarium oxysporum* liquid culture.[109] Studies have shown that Nep1-like proteins induce rapid proteomic and metabolomic changes in plant cells. For example, Villela et al. used proteomic and metabolomic methods to demonstrate the reordering of cellular processes in response to Nep1-like proteins, providing insights into NLP-mediated cell death signaling in plants.[110] A polypeptide fragment of the Nep1-like protein has been found to triggered an immune response in *Arabidopsis thaliana*, acting as a pathogen-associated molecular pattern (PAMP).[111] Advancements in understanding NLP-mediated signaling in plants will contribute to a broader comprehension of their role as biostimulants and their potential applications in agriculture.

Botrytis cinerea, a pathogen, can trigger the immune response of plants. Studies have shown that BcGs1, a protein derived from *Botrytis cinerea*, can trigger the defense response in tomatoes by activating oxygen metabolism and phenylpropane

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metabolism. This activation leads to an increase in reactive oxygen species, enhanced activity of phenylalanine ammonia-lyase and peroxidase, promotion of lignin accumulation, and improved resistance of tomatoes to gray mold.[112] XEG1, a glycosyl hydrolase from the GH12 family found in *Phytophthora sojae*, is another protein biostimulant that induces immune responses in plants. It triggers reactive oxygen species bursts, callose deposition, high expression of disease-resistant genes, and allergic necrosis. The plant cell membrane coreceptor protein BAK1 recognizes XEG1 and interacts with other receptor proteins to induce plant immunity. Further studies have identified RXEG1 as the specific receptor for XEG1, binding and activating the immune pathway.[113] XEG1 is a widely found plant immune stimulator present in Phytophthora, fungi, and bacteria.[114] The widespread presence of protein biostimulants in plants and their ability to confer disease resistance highlight the potential for their further development and utilization in agriculture. Continued research in this area could lead to the discovery and application of novel protein-based biostimulants for the control of plant diseases.

2.3. Oligosaccharide-Based Biostimulant. Oligosaccharide-based biostimulants are derived from various sources, such as the cell walls of pathogenic microorganisms, plants, or animal shells. Examples include amino-oligosaccharides from marine organisms, chito-oligosaccharides from crustacean shells and fungal cell walls, and oligo-galacturonic acid from tobacco cell walls.

Oligosaccharide-based biostimulants regulate the switching of plant hormone genes on and off. They promote the development of roots, stems, and leaves in crops, leading to a more developed root system.[115] In contrast, the secondary metabolites related to temperature stress, such as proline and reducing sugars, accumulated in the leaves of wheat treated with chito-oligosaccharides.[116,117] The chlorophyll content increased, leading to improved resistance to lodging, drought, and cold, as well as increased photosynthesis intensity.[118,119] These oligosaccharide-based stimulants have been found to induce plant defense responses and have been identified as exopolysaccharides, chitin, chitosaccharides, xylodextran, trehalose, laminaria polysaccharide, etc.[46,51] Oligosaccharide-based stimulants can also induce phenotypic changes in plants. For example, the use of amino-oligosaccharides on tobacco[120] and cucumber[121] induced physiological and biochemical changes, as well as cell wall thickening the formation of mastoids, thereby improving disease resistance. Laminaria polysaccharide can induce a wide range of defense responses in tobacco, including the release of hydrogen peroxide (H_2O_2), high levels of phenylalanine ammonia-lyase (PAL) activity and salicylic acid (SA) content, as well as the accumulation of pathogenesis-related (PR) proteins.[122] It has been shown to enhance tobacco resistance to *Erwinia carotifolia*.[123] The expression of these genes linked to defense against pathogens is inferred from the induction of these defense-related genes by laminaria polysaccharides activating a signal transduction network within grape cells. One potential method for managing diseases in grape cultivation is the application of laminaria polysaccharides, which activate defense pathways.[124]

Alginic acid is a natural polysaccharide carbohydrate that is widely found in the cell walls of brown algae. It has demonstrated encouraging results in agriculture, particularly in terms of boosting crop quality, raising productivity, strengthening disease resistance, and fostering stress tolerance, along with its oligosaccharide derivatives, alginic oligosaccharides.[125] Brown algal oligosaccharides can act as signaling molecules in plants, activating the plant's immune system and enabling it to resist bacteria and viruses.[126] As a result, fewer pesticides may be required. Furthermore, these oligosaccharides promote the synthesis of defense enzymes, hormones, and osmotic regulators in plants, all of which increase the plant's resistance to adverse environments.[127,128] Brown algal oligosaccharides enhance immune resistance through a mechanism that is reflected in multiple ways.[129] These oligosaccharides greatly lengthen and increase the number of roots under stressful conditions, which enhances the plant's ability to absorb nutrients and maintain general health.[130] In recent years, there has been a shift in the research and development of seaweed extracts, moving from mixtures to focusing on individual substances. This approach holds great prospects for the future of seaweed-based agricultural preparations.

Chitosan is derived from the deacetylation of chitin, while chitosan oligosaccharide is the degradation product of chitosan.[131] Low molecular weight chitosan and chitosan oligosaccharides show good water solubility, which makes them widely used in agricultural production, in contrast to chitin and high molecular weight chitosan, which have poor solubility.[131,132] Chitin, chitosan, and their derivatives serve as biostimulants and offer several benefits in agriculture.[133] They improve plant photosynthesis, encourage root development, induce plant disease resistance, control crop growth, and increase nutrient absorption by increasing the permeability of plant cells.[119,133,134] Furthermore, chitosan can effectively improve soil aggregate structure and has inhibitory effects on pathogen growth in the soil, which can increase crop yield and quality.[135,136] This property of chito-oligosaccharides is gaining traction in agricultural applications and has great potential in the pesticide business.

To sum up, as biostimulants in agriculture, chitosan, chitosan oligosaccharides, and chitin derivatives have several benefits. Their capacity to improve nutrient absorption, promote root development, enhance disease resistance, and contribute to soil health makes them essential instruments for sustainable agriculture methods. Furthermore, it appears that chito-oligosaccharides, in particular, may improve plant immunity and lessen the need for chemical pesticides.[137]

2.4. Metabolites-Based Biostimulants. Plant secondary metabolites play a crucial role in various aspects of plant science and chemistry.[138] These small molecular compounds are not essential for basic metabolic processes but have significant implications for studying plant phylogeny and understanding plant immune responses.[139,140] Secondary metabolites are often associated with plant disease resistance, as their accumulation is linked to immune responses.[141,142] These secondary metabolites may function as feedback regulators in the development of plant immunity and can activate signaling pathways related to plant immunity. Indeed, the promotion of plant growth, stress tolerance, and disease resistance is all aided by microbial secondary metabolites. After entering the plant rhizosphere, beneficial bacteria have the ability to control the microbial community in the soil and generate a wide range of secondary metabolites as they develop and reproduce.[56] These microbial metabolites have several beneficial effects on soil health and plant growth. They can stimulate changes in soil structure, enhance soil respiration and water retention, increase microbial populations in the soil, and promote the activities of beneficial microorganisms.[143]

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Furthermore, they provide a range of nutrients and metabolic products that support the control of the growth and development of microbial organisms.[144] Microbial secondary metabolites ultimately contribute to crop growth and yield increase by altering the soil microbiome.[145,146]

Currently, specific active compounds have been identified from microbial secondary metabolites. For instance, from the ethanol extracts of secondary metabolites of *Paecilomyces wani*, disease-resistant substances like 2′-deoxyguanosine[72] and guanine,[73] have been identified. These substances exhibit broad-spectrum disease resistance by activating plant hormone pathways through PTI (PAMP-triggered immunity) coreceptors and regulating plant disease resistance through classical PAMP responses. The identification and comprehension of these particular active chemicals shed light on the processes underlying plant disease resistance mediated by microbes and underscore the possibility of using microbial secondary metabolites as biostimulants in agriculture.

2.5. Inorganic Substance, Organic Compounds, and Microbial Inoculant. Phosphate is a traditional example of an inorganic salt biostimulant. Phosphite has been wildly used for alleviating the diseases caused by oomycete, fungi, and pathogenic bacteria.[147,148] Phosphate has been used as a fungicide since 1977, when it was found to protect crops from diseases, particularly fungal diseases.[149,150] Because phosphates also provide phosphorus and are less polluting to the environment, their compounds have been further developed and utilized.[151] Phosphate is considered an environmentally friendly agrochemical and efficient biostimulant that provides essential nutrients to enhance crop yield and quality[152] while also improving crop resistance to biological stress.[153] It has a wide range of applications across various crops. The mechanism through which phosphate activates plant defense is being gradually analyzed in the past 40 years.[154−156] Phi can directly inhibit the oxidative phosphorylation involved in pathogen metabolism.[156] Its disease resistance is attributed to the combined effects of acquired systemic disease resistance (SAR) and induced systemic disease resistance (ISR), representing a form of broad-spectrum biological control.[157] After the application of phosphorus acid to crops, it can be rapidly absorbed by crop leaves and roots, transported to the plant and play its direct bactericidal function. At the same time, it can initiate the disease resistance defense system.[153] When pathogens invade the plant, it stimulates the plant to produce plant defense hormones, thereby enhancing disease resistance. As a result, phosphate, as a biostimulant, can control disease development and improve the crop yield and quality. However, the mechanism and application of phosphate in various crops and diseases still require further refinement. In addition, the long-term effects of using phosphate biostimulants on soil, microorganisms, and the environment must be considered.

In addition, some nanomaterials have also been reported to have the function of stimulating plant defense. Du et al.'s study showed that silica nanoparticles (SiO_2 NPs) can stimulate plant immunity and protect rice from *Magnaporthe oryzae* by leaf surface treatment. Significantly reduced disease severity by nearly 70% in the appropriate concentration range.[158] Ding et al. found that CuO NPs could significantly activate the activity of a series of defense enzymes (peroxidase, catalase, chitinase, and phenylalanine aminolyase) and the expression of five resistance genes (*hrs203J*, *NmIMSP*, *PR1b*, *P450-1* and *P450-2*) in tobacco.[159] This further explains the mechanism of CuO NPs inhibiting the fungal infection of tobacco plants. The results show that CuO NPs has great potential as a nanofungicide to prevent and control diseases by inhibiting pathogen infection and stimulating plant defense resistance.[160]

Certain hormones and their byproducts can act as organic acid biostimulants to promote plant growth and defense. Early research revealed that SA can increase the accumulation of PR protein and lessen tobacco mosaic virus (TMV) symptoms.[161] In recent years, the induction mechanism of salicylic acid as a pretreated organic acid to prevent plant resistance has been gradually analyzed. In rice, SA changes the physiological function of rice by regulating the activity of photosystem II and thus induces the defense against *B. solanum*.[162] Thiadiazole-7-thioformate *S*-methyl ester (BTH), a more stable and practical salicylic acid counterpart, has been developed for SA applications.[163,164] Vernooij et al. (1994) locally inoculated tobacco plants with TMV and found that the level of endogenous SA in tobacco was significantly increased not only at the inoculated plant site but also at the noninoculated plant site.[165] Spletzer and Enyedi[166] used SA to spray tomato plants, and it was found that SA level and *PR-IB* gene expression in tomato leaves were significantly increased. These findings imply that SA derivatives can enhance plant resistance to diseases by inducing immune responses in plants as biostimulants.

S-Inducible hormone, also known as abscisic acid (ABA), is a substance that is found in a lot of plants. ABA is essential for the growth and development of plants, especially when they are exposed to unfavorable environmental circumstances. Over the past few years, more and more substances that transport immune signals over long distances like SA have been identified, including AzA,[167] glycerol-3-phosphate (G3P),[168] Pip,[169] and its derivative, NHP.[170] The function of these substances in stimulating the acquired resistance of the system has been verified. In the future, the mining of biostimulants based on plant endogenous hormones has great potential to trigger plant defense.

Over the past decade, vitamins have been found to trigger plant resistance against pathogens. There is increasing evidence suggesting that vitamins not only act as inducers of resistance but also enhance crop yield.[171,172] Thiamine, also known as vitamin B1, is the first B-type vitamin to be identified. Applying thiamine has been found to increase resistance against leaf blight in rice[173] and root-knot nematodes by promoting lignification and H_2O_2 generation. Thiamine treatment has also been found to trigger resistance against sheath blight disease in rice by increasing the accumulation of phenolics, H_2O_2 content, and the activities of PAL and superoxide dismutase (SOD).[174]

Microbial biostimulants refer to types of microorganisms that trigger plant immunity responses to various pathogens, including fungi and bacteria (e.g., members of genera *Trichoderma and Bacillus*). Agricultural microbial agents primarily refer to active biological agents produced through the fermentation of effective bacteria. Their main functions are to improve the uptake of trace elements and other nutrients by plants, to make it easier for materials to move around in the soil, to control the hormone levels in plants that encourage the release of auxin and cytokinin, and to increase resistance to abiotic stress. Consequently, the identification of exceptional strains and research on advanced fermentation processes have emerged as current areas of focus. *Bacillus subtilis* is one of the Gram-positive bacteria that has been investigated. It is widely utilized due to its high product yields, lack of toxic byproducts,

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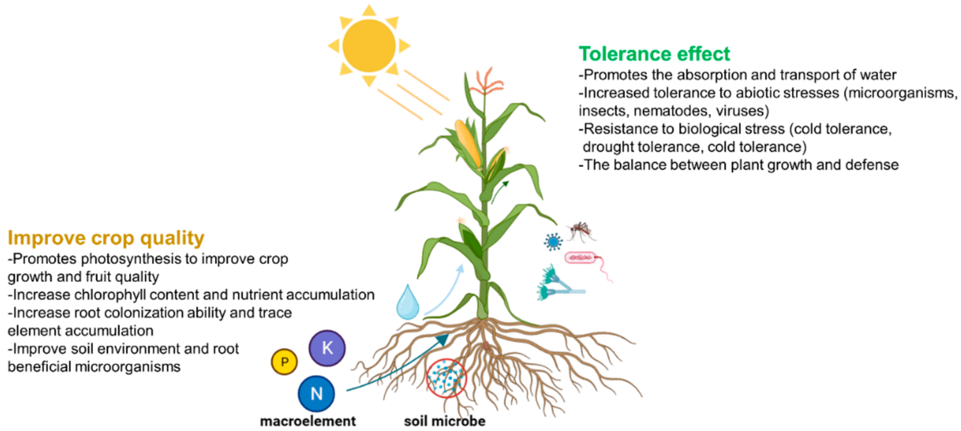

Figure 1. Mechanism of biostimulant in improving crop quality and tolerance effect.

and excellent fermentation properties.[175] For instance, the expression of the HpaG Xoc protein, a component of the harpin protein, induced a hypersensitive response and improved growth in tobacco when mediated by *B. subtilis*.[176] Several strains of *B. subtilis* have been shown to promote plant growth and to enhance plant resistance. A novel approach has recently been proposed to manage plant diseases by combining the use of the plant Pep to enhance crop resistance against plant-parasitic nematodes with the efficient delivery using *B. subtilis*.[177,178] This strategy creates new opportunities for the coapplication of beneficial microbe.

The supply of plant nutrients could promote plant growth, increase yield, and improve the quality of agricultural products and agricultural ecological environment. Arbuscular mycorrhizal fungi (AMF) are the most widely used fungi in agriculture. AMF can promote plant root growth and change plant root characteristics, which is conducive to plant absorption of more mineral elements from soil.[179] AMF also promotes plant growth and photosynthesis and enhances the capacity of the host protective system.[180] Endophytic fungi and mycorrhizal fungi interact with plants, promoting some substances such as alkaloids, JA, nitric oxide and enzymes as signaling molecules to participate in plant defense.[181] After the beneficial bacteria are added into soil, a large number of secondary metabolites are produced during the growth and reproduction process. These metabolites change of soil structure, strengthen the activities of beneficial microorganisms in the soil, produce a variety of nutrients and stimulate metabolic substances, and in turn regulate the growth and development of microbial microbial agents to promote the growth of crops.[146,182]

3. MECHANISM OF BIOSTIMULANT

The molecular mechanism and the classical pathological reactions caused by biostimulants can provide the necessary ideas for the study of their biochemistry. As shown in Figure 1, the main mechanism of biostimulants in promoting plant growth is to modify the soil environment where it is located, to activate the growth signal transduction and promote absorption of plant nutrients, and to improve photosynthetic efficiency. Biostimulants that regulate plant growth and development are also known as plant growth regulators; they function at both the molecular and cellular levels, acting as signal molecules to activate reactions both inside and outside of cells. HS-based biostimulants promote plant growth mainly by strengthening the development of plant roots.[79] On the other hand, by regulating the activity of H^+-ATPase, the absorption and transport of nutrient elements in plant roots can be enhanced to promote plant growth.[183]

Oligosaccharide-based biostimulants activated antioxidant enzyme activity and significantly upregulated expression of drought-tolerant genes in ABA signaling pathway.[184] Proteolytic enzymes can be absorbed directly by plant roots and leaves into the plant body, promoting the synthesis of proteins and other nitrogen-containing compounds and enhancing plant growth.[185] Algae extract directly stimulates the plant growth and developments by enhancing the accumulation of nitrate reductase and phosphatase in plant roots, improving the absorption capacity of plants to mineral nutrients, improving chlorophyll content, enhancing photosynthesis efficiency, improving the plant resistance to various environmental stresses and diseases and pests, and increasing crop yield.[186] Amino acids, including proline, possess chelation properties that can reduce the toxicity of heavy metals to plants, alleviate environmental stress, and also contributes to the transport and absorption of trace elements.[187]

Protein hydrolysates promote plant growth by providing nutrients and promoting plant absorption, including some inorganic substances.[188] Additionally, a plant-derived pH, Trainers, enhances the expression of the amino acid transport gene *AAT1*, improving the transport of key amino acids.[189] Furthermore, Trainers down-regulates the high-affinity nitrate transporter gene to promoting root growth.[188] Another PHs, Amino16, is thought to stimulate ammonium recycling, turnover, and amino acid remobilization, which can aid plants in reducing physiological problems brought on by too much nitrogen.[190] This notion is supported by the increased creation of chlorophylls and proteins, as well as a high sugar content, which offers carbon skeletons for protein synthesis.[191−193]

Plant hormones play a crucial role in plant adaptation to the external environment. The intricate network of hormone signaling and its interactions make it a central regulator of both the defense response and growth. In recent years, several plant hormones have been identified as having similar function to biostimulants, For example, β-amino acids (R)-β-homoserine (RBH),[194] glycerol,[195] and enzyme ascorbate oxidase (AO).[196] The regulation of the harpin protein signaling pathway is mainly controlled by various hormone signaling pathways. Recent studies have found that seaweed extracts contain a range of plant hormones that collaborate to enhance plant

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growth and increase plant stress resistance.[184,197,198] PeBL1 is a protein-based biostimulant associated with the invasion of destructive aphids. According to the study, *Sitobion avenae* was observed in wheat seedlings treated with PeBL1 to have lower fertility, significantly higher contents of JA, SA, and ET, and significantly higher accumulation of wheat seedlings compared to those not treated with PeBL1.[199] The protein inductor PevD1 isolated from *verticillium wilt* can mediate the upregulation negative regulators of ABA signaling pathway.[200]

Biostimulants increase crop yield and quality by increasing the absorption of crop nutrients and colonization of soil beneficial microorganisms, enhancing light and action. At the same time, the resistance of crops to biotic and abiotic diseases improved by increasing water absorption, triggering plant immune response, and so on. Created with Biorender.com.

With the development of science and technology, scientists have gradually analyzed the relevant mechanisms of plant immunity, and the principle of plant immunity has also been widely applied to prevent crop diseases and pests. Plants have two signaling defense mechanisms, including pathogenetic molecule-triggered immunity (PTI) and effector-triggered immunity (ETI). The first class of plant immune receptors, pattern recognition receptors (PRRs), are located on the cell membrane.[201,202] PRRs are primarily involved in the early stages of pathogen infection and provide nonhost resistance. It can resist pathogens through calcium ion flow, callose deposition, active oxygen species outbreak, stomatal closure, production of nitric oxide, and plant hormones.[203] Pathogens, in response to plant resistance strategies, secrete effectors to inhibit plant PTI. Plants have developed the second type of immune receptor, NLR (nucleotide-binding leucine-rich repeat), or ETI, to combat pathogens. ETI triggers a stronger and longer downstream immune response compared to PTI and often results in programmed cell death and anaphylaxis. Pathogens can still invade the plant by mutating effector factors, leading to a coevolutionary struggle.[204]

Decades of research have utilized chromatography to separate different components of biostimulants. In addition, living plants have been inoculated to identify allergic reactions as well as to determine the physical and chemical properties of purified biostimulants. Recently, there has been extensive research into the mechanism of biostimulant function in plant immunity. The protein polypeptide AX21 that secreted by bacteria, the cell wall component peptidoglycan, which can trigger the plant immune response.[205] In rice, CEPiB protein is responsible for recognizing fungal cell wall.[206] Biostimulants activate different immune signaling pathways to enhance plant resistance to pathogens. Certain signaling molecules, such as ROS, phytoprotectin, macromolecules, and metabolites, play a crucial role in the downstream of immune signals (Figure 2). The regulation of plant immunity by biostimulants is specific and varies between different crops and pathogens. Further research into the regulation of biostimulants on plant immunity would aid in their development and application.

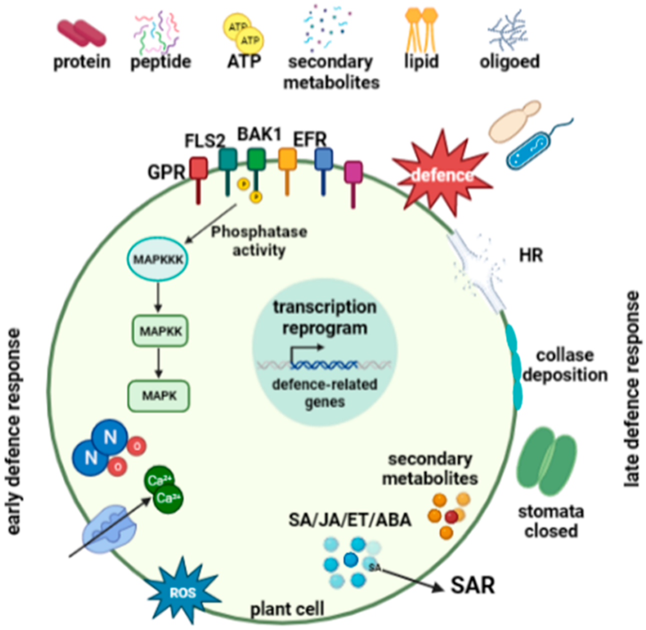

Figure 2. Mechanism of biostimulants in plant immunity. Different types of biostimulants induce plant defense responses. Receptors in plants recognize biostimulants and transmit immune signals that are amplified by a cascade of MPK signals. It causes the change of hormone signaling pathway, ROS production, callose deposition, and other PTI responses. In addition, the expression of some defense-related genes causes a downstream defense responses. The immune response also includes other signaling substances, such as nitric oxide and Ca^{2+}. Created with Biorender.com.

4. METHODS FOR THE IDENTIFICATION OF BIOSTIMULANT

Plant biostimulants are a developing field of biopesticide engineering technology. Advanced research techniques play a key role in accelerating the development of plant biostimulant products. Exploring and analyzing the molecular mechanisms of plant resistance and growth trade-offs can aid in the development of new products and the cultivation of high-quality, broad-spectrum resistant varieties. The development of biostimulants and traditional drugs follows slightly different pharmacological approaches to screening. Biostimulant discovery is often accompanied by the discovery of interesting biological phenomena. For example, the identification of specific genes related to plant resistance through gene mapping or molecular analysis, the structural analysis of receptors related to response, and the design of targeted molecules are all new drug design strategies. However, scientific inquiry systematically explores the intriguing interactions between beneficial microorganisms and plants. Following laboratory isolation, single compounds or strains were separated by some screening techniques (such as plasma chromatography, high performance liquid chromatography, and high throughput screening),[207] strain modification or structural modification was carried out, and then biological verification was carried out. One way to search for biostimulants is by screening homologous molecules and reference compound libraries, such as molecular interactions and pathway analysis, to develop similar substances. Recent studies have shown that the conserved 24 amino acids (nlp24) in the NLP protein are sufficient to induce an immune response in plants, and the NLP recognition receptor RLP23154 was successfully identified from *Arabidopsis*.[208]

The research and development of plant biostimulant products are influenced by biological resources and technical methods. First of all, the selection of biomass resources is crucial as the first step in the development of plant biostimulant products. Cost and environmental impact are important constraints to the development of biological resources. Second, advanced research techniques and methods

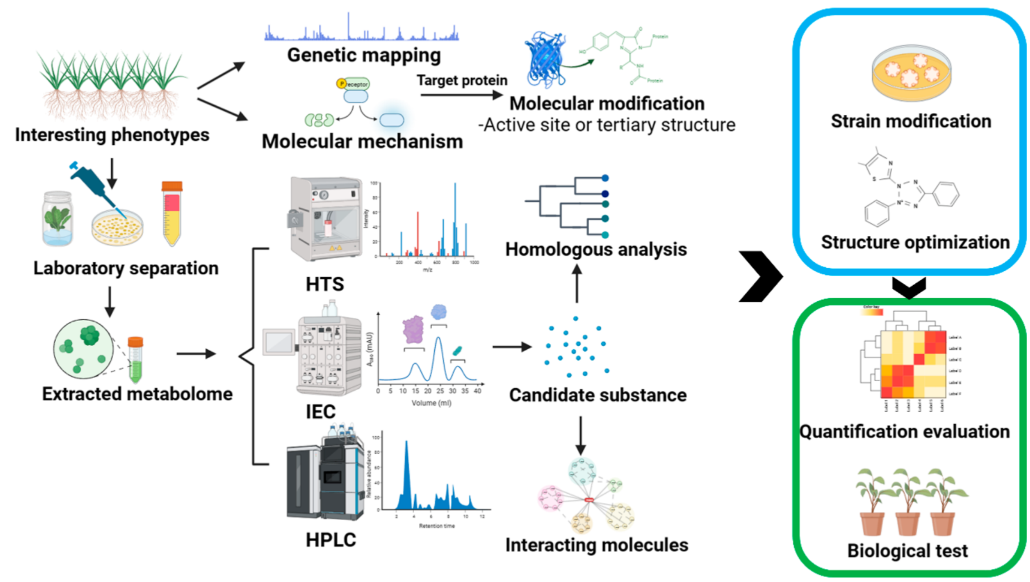

Figure 3. Development and identification of biostimulants. The infographic describes the process of developing, researching, and designing products for biostimulants, including some of the technologies involved. HTS, high throughput screening; IEC, ion exchange chromatography; HPLC, high performance liquid chromatography. Created with Biorender.com.

are another key factor in accelerating the development of plant biostimulant products. The identification technology and process of biostimulant are shown in Figure 3. Biostimulants have a significant impact on crop yields and quality throughout plant growth and development. The development of biostimulants typically follows a "pharmacological" approach, involving the screening of active substances or microorganisms under controlled conditions and progressively testing promising candidates in more realistic conditions. An alternative method is to begin with field observations and subsequently organize the scientific questions that arise in the laboratory.

5. MARKET DEVELOPMENT AND THE CHALLENGES AHEAD

The development of plant biostimulants faces several scientific, technical, and legal challenges. While the effectiveness of biostimulants is widely recognized, there are still important issues to be addressed in their development and regulation. In Europe, biostimulants are regulated through national controls on fertilizers and the European Insecticide Act. Similarly, in the United States, there is no approved definition of biostimulants, and regulations vary among the 50 states, with some relying on universal fertilizer laws to regulate specific biostimulants. The regulatory landscape is complex and lacks consistency, resulting in limited market data and reliability. In some cases, biostimulants may be subject to pesticide regulations, which further complicate their regulatory status. Once the process is recognized and registered, the prospects for enterprise development become more promising. For example, Messenger (harpin protein) produced by plant-pathogenic bacteria has played a significant role in advancing agricultural biotechnology products. In 1992, W. Zhongmin at Cornell University invented a 3% particle bioagent utilizing this protein.[209] By 2000, Messenger had successfully passed the pesticide residue test conducted by the United States Environmental Protection Agency (EPA) and was registered in the United States by Eden Biotechnology Company for application on all crops. The product received the Presidential Green Chemistry Challenge Award from the EPA in 2001 and was hailed as garnering significantly environmentally friendly plant protection and agricultural product safety. Furthermore, in 2001, the Institute for the Control of Agrochemicals, Ministry of Agriculture of China, granted a provisional registration certificate for Messenger. In 2007, the product was officially approved for use in tomatoes, peppers, tobacco, and rape. Due to its unique mechanism and proven effectiveness in disease and insect resistance, Messenger has attracted considerable attention from experts, scholars, and agricultural dealers. In July 2022, the European Union registered plant biostimulants under the new Fertilizer Regulation 2019, instead of regulating them as pesticides. The regulation defines biostimulants and outlines their four functions and classifications.

The biostimulant industry is driven by various factors, including agricultural and environmental policies, to promote sustainable agriculture worldwide. The need for efficient agricultural systems to meet future food and nonfood demands, while providing ecosystem services, is increasingly recognized. Organic farming and agroecology advocate for the use of biological solutions and materials of biological origin, aligning with the drive toward sustainable agriculture. Scientifically, understanding the complex physiological effects of biostimulants presents a challenge. Field experiments and applications play a crucial role in understanding the technology of applying biostimulants in different regions, crops, and conditions. The efficiency of nutrient use is challenging, and field measurements of plant characteristics make it challenging to determine the effects of biostimulants. Normative testing and research are needed to establish patterns and guidelines. While biostimulants are becoming increasingly popular and important in agricultural production, their market application is still somewhat limited. Biostimulants enhance plant growth by boosting the natural ability of plants to resist or overcome environmental stresses, such as heat, drought, cold, or pests. Some biostimulants are also utilized to enhance the nutritional quality and resilience of crops. Global agrochemical companies are dedicated to developing innovations that enhance agricultural production, boost farmers' incomes, and minimize

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the environmental impact of agricultural practices. As a result, agricultural industry leaders are also increasing their investments in the biostimulants sector.

6. PERSPECTIVES

Through the Web of Science database, we analyzed 1210 references pertaining to biostimulants since 2020 using VOS viewer software (Figure 4). From 2020 to the present, there

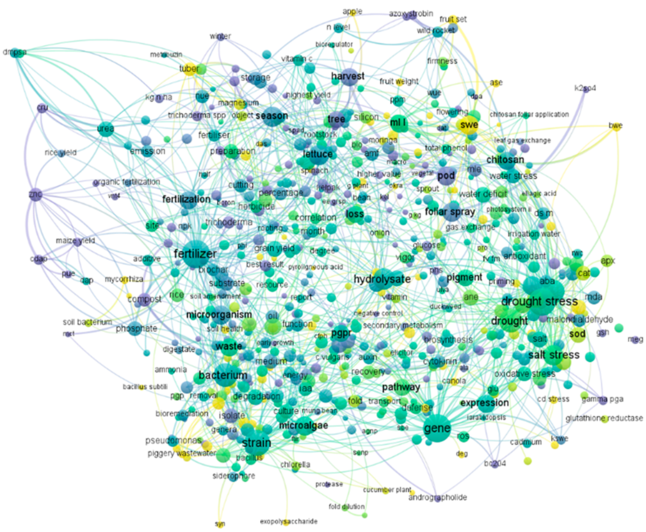

Figure 4. Map of terms of the publications on biostimulant. A visual map of 1210 biostimulant-related research articles from 2020 onward via VOS view software.

have been around 100 more published research publications about biostimulants annually than there were in 2020. From the visual analysis, the study of biostimulant is more inclined to the effect of fertilizer on plant growth and the effect on abiotic stress of plants. In recent years, the role of biostimulants in plant response to abiotic stress has been gradually explored. The benefits of biostimulants on the prevention of disease will increase in the future.

Although human immune research has a long history, the study of plant immunity is a relatively recent and less developed field. Traditionally, strategies for controlling plant diseases have focused primarily on targeting pathogenic bacteria, often overlooking the inherent resistance mechanisms present within host plants. However, by utilizing induced immune resistance in plants, we can acknowledge the natural growth patterns of plants and their inherent ability to control disease occurrences. To fully utilize this potential, it is essential to utilize the abundant resources available and conduct targeted research to develop effective and specific biological inducers. Thanks to significant scientific and technological advancements in various disciplines over the past few decades, our understanding of plant physiology has improved tremendously. Understanding the mechanisms of action of biostimulants and their interactions with environmental stresses and plant genotypes are both challenging and vital. Applying this knowledge to agricultural production holds great potential. On a practical level, it is crucial to develop tools for monitoring the efficacy of biostimulants and creating management plans to optimize their utilization. Assessing the long-term impacts on ecological services and biogeochemical cycles is crucial. By advancing research, developing effective tools, and fostering collaboration between different stakeholders, we can unlock the full potential of plant biostimulants for sustainable agriculture and disease management.

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Notes

The authors declare no competing financial interest.

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