INTRODUCTION

The current global population has reached 7.6 billion, and the per capita agricultural acreage is declining continuously, imposing a big challenge to establish fully sustainable food production systems to provide sufficient food for the growing population (Carvalho, 2017; Godfray et al., 2010; Tilman et al., 2011). However, this challenge is made more difficult by many issues, including climate change, soil environment change, resistant pests, pathogens, and weeds (Fritsche, 2018; Hollomon, 2015; Ishii, 2015; Kuck et al., 2012; Sundin & Wang, 2018). Especially in the case of pathogens, resistance continues to increase (Bauske et al., 2018; Ishii, 2015; Kuck et al., 2012; Samaras et al., 2020). Crop diseases caused by pathogens, including bacteria, fungi, viruses, nematodes, and oomycetes, are frequently encountered problems that are difficult to solve and often result in serious losses of crop production. Around 16%–20% of the worldwide crop production is lost each year due to pre-harvest diseases (Savary et al., 2019). Hence, crop protection products with novel structures...
or new mechanisms of action for creating the opportunities to address the demands of food for population growth and resistance are urgently needed.

In fact, many companies have made great efforts in the discovery of new crop protection products, such as the active ingredients discovered in recent years (Sparks et al., 2018). However, the development of products with high efficiency, high safety (including all non-targets and environment), low use rate, low resistance, and good cost-effectiveness is still a major challenge. In the following sections, we discuss the status and trends in the development of agrochemicals mainly from the perspective of microbicides, and the potential strategies that could be used as solutions for innovating agrochemicals.

2 | THE STATUS AND TRENDS OF AGROCHEMICALS

With the continuous use of pesticides, the cases of toxicity and contamination of both environment and ecology have been on the rise. Over the past decades, the use of many pesticides, such as insecticides, herbicides, and fungicides, has been prohibited globally. Moreover, there are many fungicides such as topazine, isoprothiolane, methanearsonic acid, mepronil, validamycin, iminoctadine, anilazine, oxadixyl, and metalaxyl being banned in EU countries, often because of operator safety or environmental safety. Some traditional azole fungicides, such as fluoroxyclazole, tebuconazole, flusilazole, and propiconazole, have been used as important pillars for the control of the diseases since the 1970s. However, apart from their desired antifungal properties, several azoles have exhibited endocrine disruption in mammals in vitro and in vivo (Draskau et al., 2019; Kjaerstad et al., 2010; Taxvig et al., 2007). For example, parental exposure to tebuconazole could cause thyroid endocrine disruption in zebrafish in offspring (Li, Wu, et al., 2019), and both propiconazole and tebuconazole were confirmed to show antiandrogenic effects (Taxvig et al., 2008). Because of their negative effects on the hormonal levels of human beings, some of these fungicides have already been banned, and others might be restricted or even banned in the near future. Since 2013, the EU has been preparing to review legal regulations on azoles fungicides (http://news.agropages.com/News/NewsDetail---13416.htm; Kjeldsen et al., 2013). For instance, according to the re-evaluation under the new EC regulation (No. 1107/2009) and reports from European Food Safety Agency (EFSA), propiconazole was withdrawn from use because of the following points: (Kjeldsen et al., 2013; http://news.agropages.com/News/NewsDetail---13416.htm).

- Propiconazole was classified as reproduction toxicity 1B due to its harmful effects on reproductive capacity and development;
- The maximum residue limits (MRLs) are much higher than the default value in regulation (EC No 396/2005), and the (MRLs) criteria in animal and plant products have not been validated because of the absence of toxicity data for metabolites. Therefore, the exposure level of propiconazole to humans should not be neglected;
- The metabolite (numbered as NOA436613) of propiconazole could contaminate the groundwater;
- Propiconazole may be toxic to endocrine organs, and the risk assessment related to consumers’ dietary intake cannot be completed based on the existing data.

Consequently, on 13 June 2018, the EC informed the WTO that it had recommended the discontinuation of fungicide propiconazole, implying that propiconazole will be gradually withdrawn from the EU market (http://news.agropages.com/News/NewsDetail---13416.htm).

With the implementation of the Regulation on Pesticide Administration (RPA) on 1 June 2017 (CLIC, 2019), China is expected to pay more attention to risk control measures for pesticide use. Indeed, some pesticides with potential environmental and human exposure risks have been banned by the Ministry of Agriculture (MOA) of China. For example, bismethiazol, a bactericide used against rice bacterial blight in China, was banned by MOA due to potential teratogenic effects on animals and dermatitis. In the context of revised RPA, more active ingredients with potential risk may be gradually withdrawn from the market in the future.

As shown in Figure 1, there are four stages since the birth of pesticides (Zheng et al., 2012): (1) high toxicity with low efficiency (Before the 1930s); (2) high efficiency with high toxicity (1930–1970s); (3) high efficiency with low toxicity (1970–1990s); and (4) high efficiency with both low toxicity and residue (1990s–Present). Although the pesticides of the fourth stage are obviously more acceptable by the public than before, the pesticides on this stage pay more attention to low toxicity toward human beings and low residue associated with applied objects. However, with higher and higher standards for contemporary pesticides in environmental protective systems, it is obviously harder for the pesticides of the fourth stage to completely meet the demands of modern agricultural systems. High efficiency should not only be associated with lower concentration applied and significantly controlling the effect, but also associated with high selectivity and high specificity. All non-target organisms should be considered as objects when it comes to low toxicity. Moreover, a new concept of low residue is usually related to a more thorough degradation of used pesticides, showing lower residue in the entire environment. Agrochemicals, showing high efficiency, lower use rate, high selectivity, low toxicology, low residue, low cost, user-friendly, and safety to the ecological environment, are urgently demanded (Figure 1). Although the risk management and control of pesticides are obviously difficult, implementation of some practices, such as natural products...
based, chiral compounds based, rational drug design based, and immune inducer based will benefit the economy and environment. Therefore, great efforts are required to promote research processes toward the development, application, and management of pesticides (Zheng et al., 2012).

In fact, a number of fungicides with potential high efficiency and low risks have been developed in recent years (Table 1). For instance, mefentrifluconazole and ipfentrifluconazole were discovered by the company BASF. They have shown good environmental compatibility and outstanding biological activity against fungi on field crops (e.g., corn, grain, and soybean), cash crops (e.g., green pepper, and grape), and lawn. BASF has submitted the registration data of mefentrifluconazole to EU, EPA (Environmental Protection Agency), AAFC (Agriculture and Agri-Food Canada), and management agencies in Mexico and Brazil. It was made available in 2020 and became one of the pillar products of BASF (Gu & Bai, 2018). Quinofumelin is a novel active ingredient discovered by Mitsui Chemicals Agro, Inc. (MCAG). It has novel mechanism of action and shows broad-spectrum activity against pathogens that affect trees in orchard, leafy vegetables, oilseed crops, as well as rice. It provides a unique and attractive solution for the rotational component in fungicide resistance management. Quinofumelin is under the process of registration in Japan in 2020. Oxathiapiprolin is another novel active ingredient with ultra-high efficiency against oomycete diseases in potatoes, grapes, sunflowers, vegetables, tomatoes, etc. It affects intracellular sterol transport, signal transduction, and lipid metabolism by inhibiting Oxysterol Binding Proteins (OSBP) (http://www.jsppa.com.cn/news/yanfa/1849.html; Pasteris et al., 2016). It displays good effects at all stages of the life cycle of pathogens. Its unique mechanism of action endows it with excellent efficiency against oomycetes. Oxathiapiprolin has been launched in the United States, the European Union, China, Mexico, Australia, and New Zealand (He, 2015).

China has also developed a series of fungicides including benzothiostrobin, pyrimorph, coumoxystrobin, dufulin (pronunciation of Chinese common name, similarly hereinafter), erlvjejunzuo, etc. with the support from the Basic Research Program of China (Qian et al., 2010). Their modes of action have been also investigated. For example, benzothiostrobin has a mode of action inhibiting cytochrome b transferring to cytochrome c1 within Mitochondrial Respiratory Chain, which leads to a disruption of the production of ATP (Bartlett et al., 2002; Anke, 1995). Pyrimorph could affect the biosynthesis of cell-wall in a direct or indirect way (Yan et al., 2010) through multiple mechanisms including inhibiting energy production. Dufulin, as one of the green antivirals, could induce upregulation of the pathogen-related gene and increase the activity of defense enzyme and chlorophyll content in Nicotiana tabacum K326 leaves (Li & Song, 2016). Dufulin was also targeted HrBP1 protein that could stimulate the salicylic acid (SA) signaling pathway to generate responses against viruses in host plants (Chen et al., 2012). In 2016, the National Alliance for Innovation of High Efficiency and Low Risk Pesticides was founded in Nanning, China. The alliance mainly consists of nine scientific institutes/universities, and
10 enterprises. The aim of the alliance is to gather as many superior resources as possible to develop novel pesticides with high efficiency and low risks (Anon, 2019a). Recently, a National Key R&D Program of China entitled “Development and Demonstration of Small Molecular Pesticides with High Efficiency and Low Risk”, which is hosted by Prof. Song (Guizhou University), has been initiated to investigate and develop novel pesticides including the fungicide pyrimorph and immune inducer xiangcaoliusobingmi (Shi et al., 2018; Yan et al., 2010). The ultimate goal of this program is to develop agrochemicals of “high efficiency with low risk” for crops and the application technologies for such products (Li, 2019b).

Currently, China’s MOA is strengthening the construction of risk assessment models and systems for the registration of pesticides. We predict that pesticides with potential risks will be gradually withdrawn from the market following implementation of risk assessment strategies. The new active ingredients with high efficiency and safety are expected to emerge in the future (Figure 1). In this context, the discovery and development of green pesticides is of great significance and urgency. In our opinion, the discovery and development

### Table 1: Parts of the emerged fungicides in recent years

| ISO Name | Chemical name | Company | Ref. |
|----------|---------------|---------|------|
| Mefentrifluconazole | (2RS)-2-[4-(4-chlorophenoxy)-2-((trifluoromethyl)phenyl)-1-((1H,1,2,4-triazol-1-yl)propan-2-ol | BASF AG | Gu and Bai (2018); He (2015); AWD |
| Ipentrifluconazole | α-[4-(4-chlorophenoxy)-2-((trifluoromethyl)phenyl)]-1H-1,2,4-triazole-1-ethanol | BASF AG | AWD |
| Quinoformelin | Quinoline,3-(4,4-difluoro-3,4-dihydro-3,3-dimethyl-1-isoquinolinyl) | Mitsui Chemicals Agro, Inc. | AWD |
| Dichloflubenzox | 3-[(3,4-dichloro-5-isothiazolyl)methoxy]-1,2-benzisothiazole 1,1-dioxide | Kumiai Chemical Industry | AWD |
| Fenpicoxamid | [(4-methoxy-2-)[(3S, 7R, 7S) 7-methoxy-2-[[3(3H)triazolyl)methoxy]-1,2-benzisothiazole 1,1-dioxideethyl]-1, 5-dioxoan-3-y1] amino[ carbonyl]- pyridinyl] oxy] methyl 2-methylpropanoate | Dow AgroSciences | AWD |
| Aminopyrifen | 4-phenoxybenzy12-amino-6-methyl nicotinate | Agro-Kanesho Japan | AWD |
| Pydiflumetofen | 3-(difluoromethyl)-N-methoxy-1-methyl-N-(1,2,4,6-trichlorophenyl)propan-2-yl-1H-pyrazole-4-carboxamide | Syngenta | Gu and Bai (2018); AWD; Zheng (2019) |
| Fluxapyroxad | 3-(difluoromethyl)-1-methyl-N-(3′,4′,5′-trifluorobiphenyl-2-yl)pyrazole-4-carboxamide | BASF AG | Gu and Bai (2018); AWD; Zheng (2019) |
| Fluindapyr | rac-3-(difluoromethyl)-N-[3R)-7-fluoro-1,1,3-trimethyl-2,3-dihydro-1H-inden-4-yl]-1-methyl-1H-pyrazole-4-carboxamide | Isagro S.p.A. and FMC Corporation | Gu and Bai (2018); AWD, Khetarpal (2018) |
| Inpyrfluxam | 3-(difluoromethyl)-1-methyl-N-[3R)-1,1,3-trimethyl-2,3-dihydro-1H-inden-4-yl]-1H-pyrazole-4-carboxamide | Sumitomo Chemical Co., Ltd. | Gu and Bai (2018); AWD, Khetarpal (2018) |
| Isoflucypram | N-[5-chloro-2-(1-methylethyl)phenyl]methyl-N-cyclopropyl-3-(difluoromethyl)-5-fluoro-1-methyl-1H-pyrazole-4-carboxamide | Bayer Crop Science AG | Gu and Bai (2018); AWD |
| Pyrapropone | N′-[(2Z)-2-[3-chloro-5-(2-cyclopropylethynyl)pyridin-2-yl]-2-{[(propan-2-yloxy)imino]ethyl}-3-(difluoromethyl)-1-methyl-1H-pyrazole-4-carboxamide | Nissan Chemical Industries, Ltd. | AWD |
| Picarbutrazox | 1,1-dimethylethyl n-(6-(((1-(1-methyl-1H-hexazol-5-yl)phenyl)methylene)amino)oxy)methyl]-2-pyridinyl) carbamate | Nippon Soda CO., LTD | AWD |
| Oxathiapiprolin | 1-(4-((4-(2,6-Difluorophenyl)-4,5-dihydroisoxazol-3-yl)thiazol-2-yl)piperidin-1-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)ethan-1-one | Bayer AG | Gu and Bai (2018); He (2015); AWD |
of green pesticides should be carried out by modifying natural products (NPs), chiral compounds, rational design, and plant immune agents (Figure 1, see the bottom part).

3 | THE IDENTIFICATION OF ACTIVITY OF NATURAL PRODUCTS IS A KEY DRIVER IN THE DESIGN OF NEW CHEMICAL CONTROL PRODUCTS

Many fungicides such as hymexazol, ethlycin, strobilurins, fenpiclonil, and fludioxonil are derived from the structures of NPs (Liu & Li, 2003). In recent years, the innovation of new germicidal molecules based on the structures of NPs has received widespread interest. Many natural products, such as ferulic acid (Wu et al., 2017), chalcone (Gan et al., 2017a), vanillin (Zhang, Zhao, et al., 2017), matrine (Ji et al., 2018; Li et al., 2018; Ni et al., 2017), drimane meroterpenoid (Zhang, Li, et al., 2017), lycoris alkaloids (Hu et al., 2018), etc. have been used to innovate fungicides, because of the NPs-based products showing excellent activity. For instance: (1) The matrine-based structures were found to possess high fungicidal activity against Corynespora cassiicola, Phytophthora capsici, Sclerotinia sclerotiorum, Rhizoctonia solani, and Botrytis cinerea (Ji et al., 2018; Li et al., 2018; Ni et al., 2017); (2) Zhang, Li, et al. (2017) synthesized a series of drimane meroterpenoid chiral derivatives which displayed higher antifungal activity against Botrytis cinerea than commercial carbendazim (Figure 2a); (3) It was reported that lycoris alkaloids have excellent fungicidal activity, and the modification of its structure is likely to lead to the discovery of new chiral fungicides (Figure 2b) (Hu et al., 2018); (4) Recently, Song and co-workers introduced oxadiazole and sulfonyl groups at the position of the acid moiety as a modification and derivation of gallic acid, which showed significantly high antibacterial and antifungal activity (Chen et al., 2007; Li et al., 2013, 2014; Xu et al., 2011, 2012). Consequently, jiahuangxianjunzuo, fubian’ezuofeng have been identified from the screening of thousands of compounds (Figure 2c) (Chen et al., 2007; Li et al., 2013, 2014; Xu et al., 2011, 2012). These compounds have potent antifungal and antibacterial activity and are benign to the environment and ecological systems (Meng et al., 2020; Rong et al., 2015). The industrialization and registration of such products are underway in China.

More recently, studies have identified many novel structures with excellent activity to pathogenic microorganisms, such as caffeic acid, 3,4-dicaffeoylquinic acid, 1,5-dicaffeoylquinic acid, trans-cinnamaldehyde, (-)-menthone, benzofurans, crinpellins, and (+)-yahazunol (Figure 2d) (Chen et al., 2013; Gehan & Samir, 2017; Han et al., 2018; Loiseleur, 2017; Ruiz-Vasquez et al., 2018; Sparks et al., 2017; Zhang, Wang, et al., 2018). Zhang, Wang, et al. (2018) developed a scalable
method for synthesizing (+)-yahazunol and other related meroterpenoids (Figure 2d, bottom part). The findings above indicated that these structures can be used as lead structures that were obtained by various ways and means with certain biological activity and chemical structure for further structural modification to control pathogenic microorganisms.

4 | CHIRAL COMPOUNDS HAVE HIGH POTENTIAL AS AGROCHEMICALS

In the early stage, the creation of crop protection products was usually based on simple molecules, including inorganic compounds and simple organic compounds. However, with increasing pressure from pests and diseases, more complex molecules containing an asymmetric center, have been largely investigated than before. On the one hand, some chiral products have shown significantly biological activities and been marketed with widespread application, which encourages more attention of pesticide researchers to chiral synthesis. On the other hand, in many cases, natural compounds were used as an inspiration for the creation of biological molecules, and many natural compounds own one or more chiral centers. Recently, great progress has been made in understanding the generation process and degradation mechanism of pesticides in the target organism, which makes the object research transition to the molecular structure to design the bioactive molecules based on the receptor molecules of the target organism. Since the target organisms are chiral biochemical systems, chiral pesticides are more likely to be effective. Given an asymmetric center of molecules structure, chiral agrochemicals could lead to several potential stereoisomers, including enantiomers and diastereomers. These stereoisomers could have identical physical and chemical properties but show different effects in asymmetric interactions and metabolic processes, which could lead to totally different biological activity toward pests and plant diseases (Bielská et al., 2020). However, limited by cost and synthetic methods, many chiral agrochemicals have been launched as racemic mixtures of enantiomers or diastereomers, though the biological activity and efficacy of the substance mostly rely on one or some stereoisomers in the mixture. As summarized by Peter (2018), just 5.5% of new products have been launched as pure enantiomers from 2007 to 2017.

Hence, the development of chiral agrochemicals is challenging. This is especially the case when selective preparation of enantiomers or their separation on an industrial scale is required. Peter (2018) identified that five methods can be applied for these purposes. Among them, “use of chiral building blocks” and “catalytic asymmetric synthesis” are the most common methods for producing innovative pesticides. Several chiral building blocks can be employed, and examples of such NPs are shown in Figure 2. Wang et al. developed chiral compounds using chiral NPs as the starting materials (Li et al., 2018; Li et al., 2018; Ni et al., 2017). Li et al. also used the chiral molecules derived from NPs (Zhang, Li, et al., 2017, 2018; Zhang, Wang, et al., 2018). Since 2009, Song and co-workers have been attempting to develop chiral antiviral agent by constructing a series of chiral phosphonate moieties using inexpensive, commercially available chiral amine (Chen et al., 2009), (R,R)-1,2-diaminocyclohexane (Yang et al., 2011) and L-Boc-leucine (Liu et al., 2010) as the chiral building blocks. Recently, Li and co-workers synthesized two chiral succinate dehydrogenase inhibitors (SDHIs), (R)-2-chloro-N-(2-(4-ethyl-4,5-dihydrooxazol-2-yl) phenyl)nicotinamide (SDHIs-1) (Li et al., 2016) and N-(2-(R)-4-ethyl-4,5-dihydrooxazol-2-yl) phenyl)-2-hydroxy-2-phenylacetamide (SDHIs-2) (Zhang, Li, et al., 2018) using chiral building blocks. SDHIs-1 displayed excellent fungicidal activity against Rhizoctonia solani, Botrytis cinerea, with EC50 values of 0.58 and 0.42 mg/L, respectively, which are much lower than that of non-chiral commercialized SDHIs fungicide “boscalid” (1.59 and 1.66 mg/L). SDHIs-2 showed only slightly lower activity (EC50 = 2.95 mg/L) against B. cinerea than “boscalid”.

On the other hand, “catalytic asymmetric synthesis” has shown efficient in the preparation of chiral pesticides and has been successfully applied in the synthesis of herbicide (S)-metolachlor (Peter, 2018). Recently, this strategy was adopted directly to construct molecules with agrochemical activity. For example, chiral α-amino-phosphonates with excellent activity were prepared using chiral thiourea as the organocatalyst (Zhang et al., 2016). N-Heterocyclic carbene (NHC) organocatalysis could be used in the synthesis of various bioactive chiral molecules including tricyclic sulfonamide (Zheng et al., 2015), 2-pyrylnaphosphonates (Sun, He, et al., 2018), and α-amino-phosphonates bearing sophisticated multi-cyclic scaffolds (Sun, Mou, et al., 2018). These chiral compounds provide much stronger antimicrobial activity against Xanthomonas oryzae pv. Oryzae (X. oryzae) compared to the commercial bismethiazol (Sun, He, et al., 2018; Sun, Mou, et al., 2018; Zheng et al., 2015). Although these chiral compounds are far from being effective bactericides, their structures are novel and they can be regarded as chiral lead compounds for further optimization and derivatization. Highly enantioselective compounds have shown high potential for developing innovative agrochemicals.

5 | RATIONAL DESIGN WILL CONTINUE TO LEAD INNOVATION OF AGROCHEMICALS

According to the statistic in 2005, the price for the development of a new pesticide could reach up to $256 million
(Lamberth et al., 2013). It is currently challenging to develop strategies that improve the efficiency of discovering candidate molecules. Over the past few decades, scientists have attempted to identify shortcut avenues to design compounds with high activity. The molecule modeling, including Computer-Aided Design (CAD) provides an efficient tool for drug discovery and development. “Ligand-based design” and “fragment- and target-based design” are the two important strategies (Figure 3) (Sun, 2015).

QSAR was the earliest ligand-based design method that has been used in the discovery of new pesticides (Hansch & Fujita, 1995; Plummer, 1995). It is an important “ligand-based design” tool for optimizing and developing active agrochemical structures using the information derived from the models (Figure 3a). Many active compounds have been obtained based on the information derived from CoMFA and CoMSIA models, which lay a good foundation for the further designing of drugs against pathogenic bacteria (including plant virus) (Plummer, 1995; Wu et al., 2017; Xu et al., 2012).

Fragment-based drug design (FBDD, Figure 3b) could simplify the new drug discovery process that starts from target validation, with which 20 candidates were developed and applied through FBDD in a clinical trial so far (Lamberth et al., 2013; Velvadapu et al., 2015, Chap. 7). For instance, Hao et al. (2012) discovered a picomolar inhibitor targeting cytochrome bc1 in vivo using a pharmacophore-linked fragment virtual screening (PFVS) strategy in 2012. PFVS method has been further developed into a web server ACFIS (Auto Core Fragment In silico Screening) by Yang’s group since 17 July 2014 (http://chemyang.ccnu.edu.cn/ccb/server/ACFIS/index.php; Hao et al., 2016). Recently, a novel SQR (succinate-ubiquinone oxidoreductase) inhibitor (named flubeneteram) was designed using ACFIS server and will soon be launched as a fungicide in China (Xiong et al., 2017). Recently, Yang et al. (2018) have built a special molecular database for biological-functional molecular fragments, which was called PADFrag (Pesticide and Drug Fragment). This database (http://chemyang.ccnu.edu.cn/ccb/database/PADFrag/) was set up by collecting, calculating, structure cutting, and assembling the structures of commercial drug and pesticide (FAD and Alan Wood). It was designed to accelerate the discovery of new scaffolds and establish a bridge from fragments to new scaffolds. Another rational design case is the cytochrome bc1 inhibitor developed using a substitution optimization strategy named CSO (Computational Substitution Optimization) (Hao et al., 2015). This strategy can not only make computational substitution automatically available, but also run energy minimization and binding affinity evaluation by default, which was incorporated into a web server (AIHO, Auto In Silico Optimization) (Anon, 2019b). Within the design of drug and agrochemicals, this server could work as a general method for hit to lead (H2L) optimization. In addition, there are also some potential targets for the drug design.

**FIGURE 3** The diagrammatic sketch of rational design for fungicide. (a) Ligand-based design, and (b) Fragment- and Target-based design.
Using FgMyo1 inhibitor as a potential target, Fu et al. (2020) combined molecular modeling strategies among homology modeling, molecular docking, molecular dynamics (MD) simulations, and variable dielectric molecular mechanics to obtain a novel phenamacril derivative, a species-specific novel antifungal compound, which showed higher activity than that of phenamacril against conidial germination of Fusarium graminearum. Moreover, there are also other studies targeting some enzymes such as the cytochrome P450-dependent sterol 14α-demethylase, to design antifungal molecules (Chen et al., 2018). Although there are few successful cases of rational design of pesticides, the success in medicine (Lamberth et al., 2013; Velvadapu et al., 2015) and some establishments of relevant methods related to agrochemicals could provide rich experiences and a good foundation. Moreover, other tools like AIMMS (Auto In Silico Macromolecular Mutation Scanning) (Anon, 2019c), FungiPAD (Wang et al., 2019a), scaffold hopping (López-Ramos & Perruccio, 2010), homology modeling (Orry & Abagyan, 2012) may provide useful information and techniques for agrochemicals rational design. A large number of protein structures in the public domain (www.pdb.org) and the progress in gene sequencing, and resistance are likely to boost the efforts of developing the rational design for agrochemicals. Valuable information may be derived from the newly developed virtual screening platforms to aid the rational design of agrochemicals.

6 | PLANT IMMUNE AGENTS WILL BE MORE POPULAR

In 2002, Sheen and co-workers reported the signaling process used by plants to facilitate effective protective mechanisms against pathogens (Asai et al., 2002). In 2006, Jones and Dangl (2006) proposed the concept of a plant immunity system. Subsequently, Shen et al. (2007) demonstrated that plants have special immunosensors for recognizing bacteria, viruses, and fungi infections. Methyl salicylate is an important mobile signal that mediates systemic acquired resistance in plants. It can be applied as an antidisease immune activator (Park et al., 2007). In plants, resistance signals can be triggered by exogenous substances which are then transmitted to the whole plant via endogenous signal transduction substances such as SA, jasmonic acid (JA), ethylene (ET), and nitric oxide (NO). This induces changes in defense enzymes (phenylalanine ammonia lyase, β-1,3-glucanase, chitinase, peroxidase), disease-resistant substances (lignin and phytoalexins), and other pathogenesis-related proteins (PRPs) in host plants through regulation and expression of disease resistance-related genes, thereby resisting the invasion of pathogens and reducing the occurrence of diseases (Figure 4) (Qiu, 2014; Stotz et al., 2014). Moreover, exogenous substances can stimulate the metabolic control systems in plants, promote the growth of plant roots, stems, and

FIGURE 4 The diagrammatic sketch of plant immune resistance induced by exogenous substances
leaves, and increase chlorophyll content and crop yield (Qiu, 2014). Scientists have exploited this property to develop new elicitors that activate pathogen resistance to control diseases in crops.

Accordingly, the research on plant immune agents has increased in recent years. More than 20 substances have been used as potential plant immune inducers, which have been approved in many countries (Table 2). For example, “Messenger” generated from Harpin protein in Erwinia amylovory has been widely used to control powdery mildew on citrus, pepper, tomato, cucumber, and strawberry (Wang, 2019b). “LifeGard” has an active ingredient that is Bacillus mycoides isolate J, which was identified as a catalyst for the plant’s natural immune response to fungi, viruses, and bacteria, and approved by Environmental Protection Agency (EPA) (the U.S., 2019). In 2017, “LifeGard” was shown to be safe for bees and could be applied on the day of harvesting. Acibenzolar-S-methyl, a commercial brand called “Actigard” (http://news.agropages.com/News/NewsDetail---3298.htm), is an immune inducer listed in Canada in 2011 and showed excellent synergism with fungicide for controlling tomato bacterial speck and tobacco blue mold. It mimics the natural resistance activator and enables crops to initiate defense mechanisms.

In recent years, the discovery of agrochemicals with potential plant immune-inducing activity has been an active research area in China. A new category of multi-functional biological products, protein elicitors, oligosaccharides, S-ABA, Bacillus subtilis, amino oligosaccharide, Jiasaiyouan, mushroom polysaccharides, validamycin, matrine, dufulin, and fuzuohouhuaizhi (FBT) have been approved by the MOA of China (Table 2), which have been widely applied in China. PeaT1 is a typical protein elicitor (Liu et al., 2009; Zhang et al., 2010), and the main active ingredient of “plant activates protein”. It was isolated from Alternaria tenuissima by the Institute of Plant Protection, Chinese Academy of Agricultural Sciences. PeaT1 can induce tobacco resistance to the tobacco mosaic virus (TMV) and improve the drought resistance of rice. Recently, some molecules based on natural products were synthesized by Guizhou University, which induced resistance and enhanced plant tolerance to pathogenic microorganisms (Gan et al., 2017b; Shi et al., 2018; Xie et al., 2018; Yin et al., 2018). These molecules could work in activating plant resistance. Interestingly, a trans-ferulic acid derivative containing a chalcone moiety increased the expression of proteins involved in the photoreaction system, decreased TMV infection by activating the immunity system, and higher TMV infection tolerance in plants (Gan et al., 2017b). Xiangcaoliusobingmi (Zhang, Zhao, et al., 2017), a vanillin-based agrochemical candidate developed in China, showed excellent antiviral activity against Capsicum annuum L. via enhancing the enzyme activities of peroxidase (POD), phenylalanine ammonia lyase (PAL), superoxide dismutase (SOD), and catalase (CAT). It can also improve the expression of defense-associated genes, and trigger the abscisic acid (ABA) pathway (Shi et al., 2018).

Given the recent advances in the molecular mechanisms of immune-induced resistance, botanists have gained a better understanding of how plants trigger defensive responses and the associated signaling pathways (http://news.agropages.com/News/NewsDetail---29511.htm; http://news.agropages.com/News/NewsDetail---29003.htm; Ma et al., 2017; Zhou & Wang, 2018). These studies will provide a guideline for the synthesis of immune inducers. By the way, triggering plant immune response is a well-known and well-studied target, which is a viable target for chemical interception and plant breeding. The latter has also been widely investigated for the breeding of disease-resistant crops as a crucial tool to control pathogens. For instance, Silva et al. (2018), have reviewed the biotechnological potential of molecules implicated in the different layers of plant immunity to be applied in the development of disease-resistant genetically modified (GM) plants.

7 | CONCLUSIONS AND FUTURE OUTLOOK

Facing an increasing global population and higher standards of food safety, many complex and changeable factors including extreme climate, ecological deterioration, high agrochemical resistance, and crop diseases from pests, weeds, and pathogenic microorganisms have posed a great challenge. There is an urgent need to develop appropriate strategies to address these challenges.

How do we overcome these challenges? Given their high environmental toxicity and non-target risks, some commonly used agrochemicals are no longer suitable. Nowadays, agricultural practices require agrochemicals with high efficiency, lower use rate, high selectivity, lower toxicology, low residue, cost-effectiveness, user friendly, and high environmental and ecological safety properties. It is worth noting that crop protection efforts from industry and academia have led to the design of fungicides with desirable characteristics. Several novel natural molecules have been discovered and used as active compounds. Novel chiral scaffolds with excellent activity have been developed, and rational design tools for agrochemicals have been proposed and applied. In particular, research in the field of plant immune inducers presents new opportunities for ecological agriculture. The discovery of plant immune inducers has been an important revolution in the crop protection industry and is expected to become a new approach to design antimicrobial agents for crops. These tools have created new opportunities for innovating agrochemicals with high efficacy and low risk. However, it is worth noting that these means and approaches only work on certain
| Common/Trade Name (active molecule or ingredient) | Development units | Types of pesticide | Mode of action |
|--------------------------------------------------|-------------------|--------------------|---------------|
| Messenger (HarpinEA) | EDEN Co., Ltd. of USA | Fungicide | HarpinEA as plant activator inducing system acquired resistance (SAR) (Fontanilla et al., 2005; Tosun et al., 2003) |
| LifeGard (Bacillus mycoides isolate J) | Certis USA | Fungicide | Foliar-applied biological plant activator induces a systemic response in plants (ISR) (http://news.agropages.com/News/NewsDetail---20647.htm) |
| KeyPlex humic acid (Humic acid) | KeyPlex Ltd. of USA | Plant growth regulator | Increases effective absorption of the crop to fertilizer (Olaetxea et al., 2019) |
| Probenazole (1,2-Benzisothiazole) | Meiji Seika Kaisha Co. Ltd. | Fungicide | Stimulates salicylic acid-mediated defense signal transduction pathway and activates host plants’ natural defense system (http://www.agroinfo.com.cn/other_detail_4879.html) |
| Serenade (Bacillus subtilis) | AgraQuest Co. Ltd. | Fungicide | Through the symbiosis in the root periphery, serenade could create a protective barrier around the root of plants (http://news.agropages.com/News/NewsDetail---34380.htm) |
| Chitosan (Polysaccharide biopolymer) | Ukseung Chemical Co. Ltd. of the republic of Korea | Fungicide and plant growth regulator | The binding of chitosan to teichoic acids, coupled with a potential extraction of membrane lipids (predominantly lipoteichoic acid) results in a sequence of events, ultimately leading to bacterial death (Raafat et al., 2008) |
| Pyraclostrobin (Methyl[2-[1-(4-chlorophenyl)-1H-pyrazol-3-yloxy)methyl]phenyl)methoxycarbate) | BASF AG | Fungicide | Inhibiting the mitochondrial electron transfer chain and disrupt metabolic activity that requires ATP (Bartlett et al., 2002) |
| Actigard (Acibenzolar-S-methyl) | Syngenta | Fungicide | Triggering natural defence mechanisms within the plant, preparing the plant to protect itself against infection (http://news.agropages.com/News/NewsDetail---3298.htm) |
| NCI (N-cyanomethyl-2-chloroisonicotinamide) | Nippon Kayaku Co. Ltd. of Japan | Fungicide | Activating systemic acquired resistance, independently from ethylene and jasmonic acid, by stimulating the site between SA and NPR1 (YASUDA et al., 2003) |
| Plant activate protein | Beijing Fenghui Huanong Biological S&T Co. Ltd. (Institute of Plant Protection, CAAS) | Plant growth regulator | Stimulating plants to produce salicylic acid and jasmonic acid, inducing immune signal transmission pathway to produce phytoalexin, sensitization related proteins, and improve the immunity and resistance of plants (http://www.agroinfo.com.cn/other_detail_5352.html) |
| S-ABA (S-Abciscic Acid) | Chengdu Institute of Biology, Chinese Academy of Sciences | Plant growth regulator | Increasing the content of endogenous ABA, induced an increase in antioxidant enzyme activity and Asr1 gene expression level (Yao et al., 2019) |
| Oligosaccharide chain protein | Institute of Plant Protection, CAAS | Antiviral agents | Stimulating plant metabolism and immune system to enhance the plant resistance (http://news.agropages.com/News/NewsDetail---10724.htm) |

(Continues)
types of the pathogen, particularly on biotrophic pathogens, while necrotrophic pathogens may not be controlled. Therefore, some specific fungicides are still urgently needed. Consequently, comprehensive and flexible application of the technologies such as asymmetric synthesis, structural natural product, rational drug design, and plant immune inducer, will boost the discovery of potential solutions to the challenges of food safety and issues pertaining to agrochemicals. In addition, the application of such technologies will promote crop health, ensure high yields, and protect the ecological systems.

TABLE 2 (Continued)

| Common/Trade Name (active molecule or ingredient) | Development units | Types of pesticide | Mode of action |
|-------------------------------------------------|-------------------|-------------------|----------------|
| Amino oligosaccharide                           | Hainan Zhengye Zhongnong High-tech Co. Ltd. | Immunity-inducer, Fungicide | Stimulating plant gene expression, producing chitinase, glucanase, defensin and PR protein to inhibit bacteria; inhibiting gene expression of bacteria, making physiological and biochemical variation of mycelium, and stimulating plant growth (https://www.chemicalbook.com/NewsInfo_7137.htm) |
| Jiasaiyouan (1,2,3-Thiadiazole−5-carboxamide)   | Lier Chemical Co., Ltd & Nankai University | Activator and antiviral agents | Inhibiting the mycelial growth of pathogenic fungi, making the mycelial distortion, and also inhibiting the germination of pathogenic fungi spores, or making spores produce spherical swelling (http://cn.agropages.com/News/NewsDetail---19456.htm). |
| Mushroom polysaccharides                       | Beijing Yoloo Pesticides Co., Ltd & Shandong Shengpeng Pesticides Co., Ltd. | Plant growth regulator, antiviral agents | Inactivating the virus activity, effectively destroying plant virus gene and virus cell, and inhibiting virus replication (https://new.nongyao001.com/show-36320.html) |
| Validamycin (Aminoglycoside antibiotic)         | Zhejiang Tonglu HuiFeng Biotechnology Co., Ltd | Fungicide | Interfere with fungal energy metabolism by inhibiting trehalase (Li, Duan, et al., 2019) |
| Matrine (Quinolizidine alkaloid)                | Beijing Multigrass Formulation Co., Ltd & Inner Mongolia Shuiaiqi Bio-tech Co., Ltd. | Insecticide | Acting by contact and ingestion in the control of red mites (http://news.agropages.com/News/NewsDetail---28112.htm). |
| Dufulin ([(2-fluorophenyl)([thiazol−14C1]4-methylbenzothiazol−2-ylamino)methyl] phosphonic acid diethyl ester) | Guangxi Tian Yuan Biochemical Co., Ltd & Guizhou University | Antiviral agents and immunity inducer | Inducing upregulation of the pathogen-related gene and increase the activity of defense enzyme and chlorophyll content in *Nicotiana tabacum* K326 leaves (Li & Song, 2016) |
| fuzuohuohuazhi (Fluoro-substituted benzothiadiazole derivatives, FBT) | Nantong ACA Group Co., Ltd. and East China University of Science & Technology | Fungicide | Activating the plant immune system by significantly increasing the activity of many enzymes in plants (Ma et al., 2019) |

Note: Abbreviation: CAAS: Chinese Academy of Agricultural Sciences.

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CONFLICT OF INTEREST
The authors declare that there is no competing financial interest.
REFERENCES

Anke, T. (1995). The antifungal strobilurins and their possible ecological role. *Canadian Journal of Botany*, 73, 940–945. https://doi.org/10.1139/b95-342

Anon. (2019a). National Alliance for Innovation of High Efficiency and Low Risk Pesticides was established. Retrieved from http://cn.агрошопages.com/News/NewsDetail—12645.htm

Anon. (2019b). (Auto In Silico Optimization) web Server. Retrieved from http://chemyang.ccu.edu.cn/ccb/server/AHIO/

Anon. (2019c). (Auto In Silico Macromolecular Mutation Scanning) web server. Retrieved from http://chemyang.ccu.edu.cn/ccb/server/AIMMS/index.php

Asai, T., Tenra, G., Plotnikova, J., Willmann, M. R., Chiu, W.-L., Gomez-Gomez, L., Boller, T., Ausubel, F. M., & Sheen, J. (2002). MAP kinase signalling cascade in Arabidopsis innate immunity. *Nature*, 415, 977–983. https://doi.org/10.1038/415977a

AWD. (Alan Wood Database) Compendium of Pesticide Common Names. Retrieved from http://www.alanwood.net/pesticides/index.html

Bartlett, D. W., Clough, J. M., Godwin, J. R., Hall, A. A., Hamer, M., & Parr-Dobrzanski, B. (2002). The strobilurin fungicides. *Pest Management Science*, 58, 649–662. https://doi.org/10.1002/ps.520

Bauske, M. J., Mallik, I., Yellareddygari, S. K. R., & Gudmestad, N. C. (2019). Fusarium graminearum through an integrated molecular modeling strategy. *Pest Management Science*, 76, 3990–3999. https://doi.org/10.1002/ps.9548

Bielská, L., Hale, S. E., & Škulcová, L. (2020). A review on the stereospecific fate and effects of chiral conazole fungicides. *Science of the Total Environment*, 750, 141600. https://doi.org/10.1016/j.scitotenv.2020.141600

Carvalho, F. P. (2017). Pesticides, environment, and food safety. *Food and Energy Security*, 6, 48–60. https://doi.org/10.1002/fe3.108

Chen, C. J., Song, B. A., Yang, S., Xu, G. F., Bhadury, P. S., Jin, L. H., Hu, D. Y., Li, Q. Z., Liu, F., Xue, W., Lu, P., & Chen, Z. (2007). Synthesis and antifungal activities of 5-(3,4,5-trimethoxyphenyl)-2-sulfonyl-1,3,4-thiadiazole and 5-(3,4,5-trimethoxyphenyl)-2-sulfonyl-00201,3,4-oxadiazole derivatives. *Bioorganization Medicine Chemistry*, 15, 3981–3989. https://doi.org/10.1016/j.bmc.2007.04.014

Chen, F. J., Long, X. H., Yu, M. N., Liu, Z. P., Liu, L., & Shao, H. B. (2013). Phenolics and antifungal activities analysis in industrial crop Jerusalem artichoke (*Helianthus tuberosus L.*) leaves. *Industrial Crops and Products*, 47, 339–345. https://doi.org/10.1016/j.indcrop.2013.03.027

Chen, L., Zhao, B., Fan, Z., Liu, X., Wu, Q., Li, H., & Wang, H. (2018). Synthesis of Novel 3,4-Chloroisothiazole-based imidazoles as fungicides and evaluation of their mode of action. *Journal of Agriculture and Food Chemistry*, 66, 7319–7327. https://doi.org/10.1021/acs.jafc.7b00958

Chen, M. H., Chen, Z., Song, B. A., Bhadury, P. S., Yang, S., Cai, X. J., Hu, D. Y., Xue, W., & Zeng, S. (2009). Synthesis and Antiviral activities of chiral thiourea derivatives containing an α-aminophosphonate moiety. *Journal of Agriculture and Food Chemistry*, 57, 1383–1388. https://doi.org/10.1021/jf803215t

Chen, Z., Zeng, M. J., Song, B. A., Hou, C. R., Hu, D. Y., Li, X. Y., Wang, Z. C., Fan, H. T., Bi, L., Liu, J. J., Yu, D. D., Jin, L. H., & Yang, S. (2012). Dufulin activates HrBP1 to produce antiviral responses in tobacco. *PLoS One*, 7, e57944. https://doi.org/10.1371/journal.pone.0037944

CLIC. (2019). *New laws and regulations*. Retrieved from China Legal Information Center. http://www.chinadaily.com.cn/m/chinalic/2017/08/21/content_30905339.htm

CPIN. (2019). *Pesticide Registration Database of China’s ICAMA*. China Pesticide Information Network. (CPIN). Retrieved from http://www.chinapesticide.org.cn/hsyj/index.html

Draskau, M. K., Boberg, J., Taxvig, C., Pedersen, M., Frandsen, H. L., Christiansen, S., & Svingen, T. (2019). In vitro and in vivo endocrine disrupting effects of theazole fungicides triticonazole and flusilazole. *Environmental Pollution* (Oxford, U. K.), 255, 113309. https://doi.org/10.1016/j.envpol.2019.113309

Fontanilla, J. M., Montes, M., & De Prado, R. (2005). Effects of the foliar-applied protein "HarpinEA" (Messenger) on tomato fruits infected with Phytophthora infestans. *Communications in Agricultural and Applied Biological Sciences*, 70, 41–45.

Fritsch, J. (2018). Recent developments and digital perspectives in food safety and authenticity. *Journal of Agriculture and Food Chemistry*, 66, 7562–7567. https://doi.org/10.1021/acs.jafc.8b00843

Fu, W. T., Wu, N. J., Ke, D., Chen, Y., Xu, T. M., & Tang, G. F. (2020). Discovery of a species-specific novel antifungal compound against Fusarium graminearum through an integrated molecular modeling strategy. *Pest Management Science*, 76, 3990–3999. https://doi.org/10.1021/acs.jafc.8b00843

Gan, X. H., Hu, D. Y., Chen, Z., Wang, Y. J., & Song, B. A. (2017b). Synthesis and antiviral evaluation of novel 1,3,4-oxadiazole/thiadiazole-chalcone conjugates. *Bioorganic & Medicinal Chemistry Letters*, 27, 4298–4301. https://doi.org/10.1016/j.bmcl.2017.08.038

Gan, X. H., Hu, D. Y., Wang, Y. J., Yu, L., & Song, B. A. (2017a). Novel trans-ferulic acid derivatives containing a chalcone moiety as potential activator for plant resistance induction. *Journal of Agriculture and Food Chemistry*, 65, 4367–4377. https://doi.org/10.1021/acs.jafc.7b00958

Gehan, I. K. M., & Samir, A. M. A. (2017). Antifungal potential and biochemical effects of monoterpenes and phenylpropenes on plant. *Plant Protection Science*, 54, 9–16. https://doi.org/10.17221/9/2017-pps

Godfrey, H. C. J., Beddington, J. R., Crute, I. R., Haddad, L., Lawrence, D., Muir, J. F., Pretty, J., Robinson, S., Thomas, S. M., & Toulmin, C. (2010). Food security: The challenge of feeding 9 billion people. *Science*, 327, 812–818. https://doi.org/10.1126/science.1185383

Gu, L. L., & Bai, Y. L. (2018). Application and development of 10 kinds of new pesticides with potential. *Mod. Agro.*, 17, 1–7.

Han, J. W., Oh, M., Lee, Y. J., Choi, J., Choi, G. J., & Kim, H. (2018). Crinpellins A and I, two diterpenoids from the basidiomycete fungus crinpellis rhizomaticola, as potential natural fungicides. *Molecules*, 23, 2377. https://doi.org/10.3390/molecules23092377

Hansch, C., & Fujita, T. (1995). *Status of QSAR at the End of the Twentieth Century, Classical and Three-Dimensional QSAR in Agrochemistry*. Chapter 1, 1995, pp 1–12.

Hao, G. F., Jiang, W., Ye, Y. N., Wu, F. X., Zhu, X. L., Guo, F. B., & Yang, G. F. (2016). Pharmacophore-linked fragment virtual screening (PFVS) is a method for drug design. *Nucleic Acids Research*, 44, 550–556. https://doi.org/10.1093/nar/gkw393

Hao, G. F., Wang, F., Li, H., Zhu, X. L., Yang, W. C., Huang, L. S., Wu, J. W., Berry, E. A., & Yang, G. F. (2012). Computational
Discovery of pimocanol Q site inhibitors of cytochrome bc1 complex. *Journal of the American Chemical Society*, 134, 11168–11176. https://doi.org/10.1021/acs.ja0031908

Hao, G. F., Yang, S. G., Huang, W., Wang, L., Shen, Y. Q., Tu, W. L., Li, H., Huang, L. S., Wu, J. W., Berry, E. A., & Yang, G. F. (2015). Rational design of highly potent and slow-binding cytochrome bc1 inhibitor as fungicide by computational substitution optimization. *Scientific Reports*, 5, 13471. https://doi.org/10.1038/srep13471

He, X. L. (2015). Novel Fungicide-oxathiapiprin. *Word Pest*, 37, 58–59.

Hollomon, D. W. (2015). Fungicide resistance: facing the challenge. *Plant Product Science*, 51, 170–176. https://doi.org/10.17221/42/2015-PPS

Hu, Z., Wang, Z. W., Liu, X. Y., & Wang, Q. M. (2018). Leveraging botanical resources for crop protection: the isolation, bioactivity and structure-activity relationships of lycoris alkaloids. *Pest Management Science*, 74, 2783–2792. https://doi.org/10.1002/ps.5065

Ishii, H. (2015). Fungicide resistance in plant pathogens: principles and a guide to practical management. *Netherlands Journal of Plant Pathology*, 87, 233–255. https://doi.org/10.1007/978-4-431-55642-8

Ji, X. F., Guo, J. C., Liu, X. Y., Lu, A. D., Wang, Z. W., Li, Y. Q., Yang, S. X., & Wang, Q. M. (2018). Marine-natural-product development: first discovery of norterpentin alkaloids as novel antiviral, anti-phytopathogenic fungus, and insecticidal. *Journal of Agriculture and Food Chemistry*, 66, 4062–4072. https://doi.org/10.1021/acs.jafc.8b00507

Jones, J. D. G., & Dangl, J. L. (2006). The plant immune system. *Nature*, 444, 323–329. https://doi.org/10.1038/nature05286

Khetarpal, N. (2018). New Fungicide discovery-IP Case study: The Curious Case of Inpyrfluxam. Retrieved from http://news.agropages.com/News/NewsDetail-27410.htm

Kjaerstad, M. B., Taxvig, C., Andersen, H. R., & Nellerm, C. (2010). International Journal of Andrology, 33, 425–433. https://doi.org/10.1111/j.1365-2605.2009.01034.x

Kjeldsen, L. S., Ghisari, M., & Bonefeld-Jørgensen, E. C. (2013). Currently used pesticides and their mixtures affect the function of sex hormone receptors and aromatase enzyme activity. *Toxicology and Applied Pharmacology*, 272, 453–464. https://doi.org/10.1016/j.taap.2013.06.028

Kuck, K. H., Leadbeater, A., & Gisi, U. (2012). FRAC mode of action classification and resistance risk of fungicides. In P. Jeschke, et al. (Eds.), *Modern crop protection compounds* (Vol. 2, 2nd ed., pp. 1238–1257). Wiley-VCH.

Lambeth, C., Jeannmart, S., Luksch, T., & Plant, A. (2013). Current challenges and trends in the discovery of agrochemicals. *Science*, 341, 724–726. https://doi.org/10.1126/science.1237227

Li, B. F. (2019b). *The National Key R&D Program “Research and Development and Demonstration of Small Molecular Pesticides with High Efficiency and Low Risk”* was launched, August 30, 2018. Retrieved from http://news.gza.edu.cn/2018/0830/c11066a102549/page.htm

Li, G., Guo, J. C., Wang, Z. W., Liu, X. Y., Song, H. B., & Wang, Q. M. (2018). Marine natural products for drug discovery: First discovery of kealiinines A-C and their derivatives as novel antiviral and antiphytopathogenic fungus agents. *Journal of Agriculture and Food Chemistry*, 66, 7310–7318. https://doi.org/10.1021/acs.jafc.8b02238

Li, J., Duan, Y. B., Bian, C. H., Pan, X. A., Yao, C. J., Wang, J. X., & Zhou, M. G. (2019). Effects of validamycin in controlling Fusarium head blight caused by *Fusarium graminearum*: Inhibition of DON biosynthesis and induction of host resistance. *Pesticide Biochemistry and Physiology*, 153, 152–160. https://doi.org/10.1016/j.pestbp.2018.11.012

Li, P., Shi, L., Yang, X., Yang, L., Chen, X. W., Wu, F., Shi, Q. C., Xu, W. M., He, M., Hu, D. Y., & Song, B. A. (2014). Design, synthesis, and antibacterial activity against rice bacterial leaf blight and leaf streak of 2,5-substituted-1,3,4-oxadiazole/thiadiazole sulfone derivative. *Bioorganic & Medicinal Chemistry Letters*, 24, 1677–1680. https://doi.org/10.1016/j.bmcl.2014.02.060

Li, P., Yin, J., Xu, W. M., Wu, J., He, M., Hu, D. Y., Yang, S., & Song, B. A. (2013). Synthesis, antibacterial activities, and 3D-QSAR of sulfone derivatives containing 1,3,4-oxadiazole moiety. *Chemical Biology & Drug Design*, 82, 546–556. https://doi.org/10.1111/cbdd.12181

Li, S. K., Li, D. D., Xiao, T. F., Zhang, S. S., Song, Z. H., & Ma, H. Y. (2016). Design, synthesis, fungicidal activity, and unexpected docking model of the first chiral boscalid analogues containing oxazolines. *Journal of Agriculture and Food Chemistry*, 64, 8927–8934. https://doi.org/10.1021/acs.jafc.6b03464

Li, S. Y., Wu, Q., Sun, Q. Q., Coffin, S., Gui, W. J., & Zhu, G. N. (2019). Parental exposure to tebuconazole causes thyroid endocrine disruption in zebrafish and developmental toxicity in offspring. *Aquatic Toxicology*, 211, 116–123. https://doi.org/10.1016/j.aquatox.2019.04.002

Li, X. Y., & Song, B. A. (2016). Progress in the development and application of plant-based antiviral agents. *Journal of Integrative Agriculture*, 16, 2772–2783. https://doi.org/10.1016/S2095-3119(17)61788-X

Liu, C. L., & Li, Z. M. (2003). Agrochemicals discovered and developed from natural leads (I)-fungicides. *Pesticides*, 42, 1–4

Liu, J. Z., Yang, S., Li, X. Y., Fan, H. T., Pinaki, B., Xu, W., Wu, J., & Wang, Z. C. (2010). Synthesis and antiviral bioactivity of chiral thioureas containing and phosphonate moieties. *Molecules*, 15, 5112–5123. https://doi.org/10.3390/molecules15085112

Liu, Q., Li, G. Y., Zeng, H. M., Yang, X. F., & Qiu, D. W. (2009). Acquisition of microbial protein elicitor PeaT1 and preliminary research on inducing drought resistance of rice. *Journal of Agricultural Science and Technology*, 11, 51–55.

Loiseleur, O. (2017). Natural products in the discovery of agrochemicals. *Chimia*, 71, 810–822. https://doi.org/10.2533/chimia.2017.810

López-Ramos, M., & Perruccio, F. (2010). HPPD: Ligand- and target-based virtual screening on a herbicide target. *Journal of Chemical Information and Modeling*, 50, 801–814. https://doi.org/10.1021/ci900498n

Ma, B., Wang, J. H., Liu, C. Z., Hu, J. F., Tan, K. F., Zhao, F. Y., Yuan, M., Zhang, J. H., & Gai, Z. J. (2019). Preventive effects of fluorosubstituted benzothiazoliazole derivatives and chitosan oligosaccharide against the rice seedling blight induced by *Fusarium oxysporum*. *Plants*, 8, 538. https://doi.org/10.3390/plants8120538

Ma, Z. C., Zhu, L., Song, T. Q., Wang, Y., Zhang, Q., Xia, Y. Q., Qiu, M., Lin, Y. C., Li, H. Y., Kong, L., Fang, Y. F., Ye, W. W., Wang, Y., Dong, S. M., Zheng, X. B., Tyler, B. M., & Wang, Y. C. (2017). A paralogous decoy protects Phytophthora sojae apoplastic effector PsXEG1 from a host inhibitor. *Science*, 355, 710–714. https://doi.org/10.1126/science.aai7919

Meng, X. G., Wang, N., Long, X. F., Chen, L. Z., & Hu, D. Y. (2020). Qualitative and Quantitative Analysis of the new sulfone
bactericide 2-(4-fluorophenyl)-5-(methylsulfonyl)-1,3,4-oxadiazole and identification of its degradation pathways in paddy water. *Journal of Chromatographic Science*, 58, 859–867. https://doi.org/10.1093/chromsci/bmaa055

Ni, W. J., Li, C. J., Liu, Y. X., Song, H. J., Wang, L. Z., Song, H. B., & Wang, Q. M. (2017). Various bioactivity and relationship of structure-activity of matrine analogues. *Journal of Agriculture and Food Chemistry*, 65, 2039–2047. https://doi.org/10.1021/acs.jafc.6b00547

Olaetxea, M., Mora, V., Baacaicoa, E., Baigorri, R., Garnica, M., Fuentes, M., Zamarreño, A. M., Spichal, L., & García-Mina, J. M. (2019). Root ABA and H+/ATPase are key players in the root- shoot growth promoting action of humic acids. *Plant Direction*, 3, 1–12. https://doi.org/10.1002/pld3.175

Orry, A. J. W., & Abagyan, R. (2012). *Homology modeling: Methods and protocols*. Humana Press.

Park, S. W., Kaimoyo, E., Kumar, D., Mosher, S., & Klessig, D. F. (2007). Methyl salicylate is a critical mobile signal for plant systemic acquired resistance. *Science*, 318, 113–116. https://doi.org/10.1126/science.1147113

Pasteris, R. J., Hanagan, M. A., Bisaha, J. J., Finkelstein, B. L., Hoffman, L. E., Gregory, V., Andreassi, J. L., Sweeney, J. A., Klyachkints, B. A., Henry, Y. T., & Berger, R. A. (2016). Discovery of oxathiapiprolin, a new oomycete fungicide that targets an oxysterol binding protein. *Bioorganic & Medicinal Chemistry*, 24, 354–361. https://doi.org/10.1016/j.bmc.2015.07.064

Peter, J. (2018). Current status of chirality in agrochemicals. *Pest Management Science*, 74, 2389–2404. https://doi.org/10.1002/ps.5052

Plummer, E. L. (1995). Successful Application of the QSAR Paradigm in Discovery Programs, Classical and Three-Dimensional QSAR in Agrochemistry. *Chapter 18*, 1995, pp 240–253. ACS Symposium Series, Vol. 606. https://doi.org/10.1021/bk-1995-0606.ch018

Qian, X., Lee, P. W., & Cao, S. (2010). China: Forward to the green pesticides via a basic research program. *Journal of Agriculture and Food Chemistry*, 58, 2613–2623. https://doi.org/10.1021/jf904098w

Qiu, D. W. (2014). Progress and prospect of plant immunity inducer. *Journal of Agricultural Science and Technology*, 16, 39–45. https://doi.org/10.13304/j.ynjdb.2014.043

Rafat, D., Bargen, K. V., Haas, A., & Sahl, H. G. (2008). Insights into the mode of action of chitosan as an antibacterial compound. *Applied and Environment Microbiology*, 74, 3764–3773. https://doi.org/10.1128/AEM.00453-08

Rong, L. H., Jin, M. J., Pan, S. Z., Zhang, J., Tang, M. M., He, J., Zhang, K. K., & Hu, D. Y. (2015). Determination and method validation of the new sulfone fungicide 2-(4-fluorophenyl)-5-methylsulfonyl-1,3,4-oxadiazole in tomato and soil by UPLC in field trial samples from Guizhou province, China. *Bulletin of Environmental and Health*, 28, 491–500. https://doi.org/10.1016/j.pestbp.2018.06.008

Samaras, A., Hadjipetrou, C., & Karagolandiis, G. (2020). Bacillus amyloliquefaciens strain QST713 may contribute to the management of SDHI resistance in *Botrytis cinerea*. *Pest Management Science*, 79, 2221. ahead of print. https://doi.org/10.1002/ps.6145

Savary, S., Willocquet, L., Pethybridge, S. J., Esker, P., McRoberts, N., & Nelson, A. (2019). The global burden of pathogens and pests on major food crops. *Nature Ecology & Evolution*, 3, 430–439. https://doi.org/10.1038/s41559-018-0793-y

Shen, Q. H., Saijo, Y., Mauch, S., Biskup, C., Bieri, S., Keller, B., Seki, H., Ulerk, B., Somschich, I. E., & Schulze-Le fret, P. (2007). Nuclear activity of MLA immune receptors links isolate- specific and basal disease-resistance responses. *Science*, 315, 1098–1103. https://doi.org/10.1126/science.1136372

Shi, J., Yu, L., & Song, B. A. (2018). Proteomics analysis of Xiangcaoliususungmii- treated *Caspicum annuum* L. infected with Cucumber mosaic virus. *Pestic. Biochem. Phys.*, 149, 113-122. https://doi.org/10.1016/j.pestbp.2018.06.008

Silva, M. S., Arraes, F. B. M., Campos, M. D., Grossi-de-Sa, M., Fernandez, D., Cândido, E. D., Cardoso, M. H., Franco, O. L., & Grossi-de-Sa, M. F. (2018). Review: Potential biotechnological assets related to plant immunity modulation applicable in engineering disease-resistant crops. *Plant Science*, 270, 72–84. https://doi.org/10.1016/j.plantsci.2018.02.013

Sparks, T. C., Hahn, D. R., & Garizi, N. V. (2017). Natural products, their derivatives, mimics and synthetic equivalents: Role in agrochemical discovery. *Pest Management Science*, 73, 700–715. https://doi.org/10.1002/ps.4458

Sparks, T. C., Hunter, J. E., Lorsbach, B. A., Hanger, G. R., Gast, R. E., Kemmitt, G., & Bryant, R. J. (2018). Crop protection discovery: Is being the first best? *Journal of Agriculture and Food Chemistry*, 66, 10337–10346. https://doi.org/10.1021/acs.jafc.8b03484

Stotz, H. U., Mitrousis, G. K., de Wit, P. J. G. M., & Fitt, B. D. L. (2014). Effector-triggered defence against apoplastic fungal pathogens. *Trends in Plant Science*, 19, 491–500. https://doi.org/10.1016/j.tiplants.2014.04.009

Sun, H. M. (2015). *A practical guide to rational drug design*. Elsevier Ltd. https://doi.org/10.1016/C2014-0-02348-9

Sun, J., He, F. C., Wang, Z. Y., Pan, D. W., Mou, C. L., Jin, Z. C., & Chi, Y. G. R. (2018). Carbene-catalyzed enal γ-carbon addition to keto-phosphonates for enantioselective access to bioactive 2-pyryliphosphonates. *Chemical Communications*, 54, 6040–6043. https://doi.org/10.1039/C8CC03017K

Sun, J., Mou, C. L., Liu, C. Y., Huang, R. Y., Zhang, S. P., Zheng, P. C., & Chi, Y. G. R. (2018). Enantioselective access to multi-cyclic α-amino phosphonates via carbene-catalyzed cycloaddition reactions between enals and six-membered cyclic imines. *Organization of Chemistry Frontiers*, 5, 2992–2996. https://doi.org/10.1039/c8qo00877a

Sundin, G. W., & Wang, N. (2018). Antibiotic resistance in plant pathogenic bacteria. *Annual Review of Phytopathology*, 56, 161–180. https://doi.org/10.1146/annurev-phyto-080417-045946

Taxvig, C., Hass, U., Axelstad, M., Dalgaard, M., Andeasen, H. R., & Vinggaard, A. M. (2007). Endocrine-disrupting activities in vivo of the fungicides tebuconazole and epoxiconazole. *Toxicological Sciences*, 100, 464–473. https://doi.org/10.1093/toxsci/kfm227

Taxvig, C., Vinggaard, A. M., Hass, U., Axelstad, M., Metzdorff, S., & Nelleman, C. (2008). Endocrine-disrupting properties in vivo of widely used azole fungicides. *International Journal of Andrology*, 31, 170–177. https://doi.org/10.1111/j.1365-2605.2007.00838.x

Tilman, D., Balzer, C., Hill, J., & Befort, B. L. (2011). Global food demand and the sustainable intensification of agriculture. *Proceedings of the National Academy of Sciences of the United States of America*, 108, 20260–20264. https://doi.org/10.1073/pnas.1116437108
