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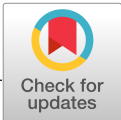
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**REVIEW**

Selecting for useful properties of plants and fungi – Novel approaches, opportunities, and challenges

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Societal Impact Statement

For millennia, humans have used plants and fungi, as foods, fuels, fibers, and medicines; and have developed techniques for improving their usefulness to our species, mostly through selection of desirable traits. With human populations forecast to rise, the availability of arable land likely to fall amid climate change and increasing urbanization, and modern communications technologies accelerating the dispersal of pathogens, further improvement is urgently needed. However, ensuring long-term resilience involves conservation of existing genetic diversity in addition to selection. New technologies, particularly those based on molecular biology, are increasingly driving conservation and improvement strategies.

Summary

Humans use plants and fungi for a wide range of purposes and, over millennia, have improved wild species by selecting for and combining genetic variation. Improvements in DNA sequencing technologies have enhanced our capacity to identify and manipulate genetic diversity, increasing the range of variation that can be utilized, and accelerating the breeding cycle to reduce the time taken to develop and put new varieties to use. Most recently, the CRISPR/Cas9 gene editing technology has greatly increased our capacity to directly introduce novel genetic variants without unwanted associated material. Moreover, increased knowledge of metabolic pathways resulting from genomic analysis can be used to design new varieties with desired properties with increased precision. Selecting for, or engineering, desirable variants has increased the usefulness of plants and fungi to humans, but at the cost of reducing their genetic diversity, decreasing their resilience and reducing the stock of variation available for future use. Conservation of genetic biodiversity is thus an essential counterpart of crop improvement and is essential to ensure that crop species retain resilience to emerging threats. Conservation efforts are focused on orphan crops, wild relatives of crop species, and landraces; *in* and *exsitu* efforts are complementary. Informatic approaches can inform use of these materials in breeding programmes even in the absence of genomic information. The application of some of

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these approaches may be restricted by ethical, legal, or organizational obstacles. If these can be overcome, there is great potential to unlock previously untapped reservoirs of biodiversity for human benefit.

KEYWORDS

breeding, conservation, crops, fungi, genetic diversity, genetic modification, metabolic engineering, plants

1 | INTRODUCTION

For millennia, humans have used plants and fungi as foods, fuels, fibers, and medicines. Early humans gathered plant and fungal materials from the wild, but agriculture has been practiced for at least 11,500 years (Fernie & Yan, 2019; Meyer & Purugganan, 2013). Humans have not only cultivated these species, but also sought, by casual selection and deliberate breeding, to improve yield, resilience to biotic and abiotic stress, and the properties of varieties under cultivation (Schlegel, 2018). Established plant breeding practices helped inform the experiments that first elucidated the genetic basis of inheritance, and this understanding has underpinned the development of modern scientific breeding programmes, in which the recorded characteristics of individuals and lines are used to develop new varieties with desirable combinations of traits (Voss-Fels, Stahl, & Hickey, 2019). More recently developed approaches exploit low-cost techniques for DNA sequencing and molecular modification tools to increase the precision with which new varieties can be created, and speeding their delivery to market (Chen, Wang, Zhang, Zhang, & Gao, 2019; Hickey et al., 2019; Lenaerts, Collard, & Demont, 2019). With human populations forecast to rise, the availability of arable land likely to fall amid climate change and increasing urbanization, and modern communications technologies accelerating the dispersal of plant pathogens, these developments are decidedly timely (FAO, 2017; Jorasch, 2019; Roell & Zurbriggen, 2020).

Although short-term improvement strategies are focused on engineering specific genotypes, maintaining biodiversity is essential to provide the genetic reservoir from which future crops will be developed (Govindaraj, Vetriventhan, & Srinivasan, 2014; Tester & Langridge, 2010). Most crop species have undergone just a few domestication events, and while repeated rounds of subsequent selection have optimized their properties, these have significantly reduced the residual genetic diversity present in current populations (Smýkal, Nelson, Berger, & Von Wettberg, 2018). Today's crops thus bear little resemblance to their wild ancestors, and their genetic homogeneity threatens our ability to breed for resilience in the face of novel threats (Dulloo et al., 2017). There is therefore increasing interest in exploring new sources of genetic variation (Castañeda-Álvarez et al., 2016; Smýkal et al., 2018). For example, there may be the potential for significant gains in yield and quality in under-utilized species that have not yet been subject to scientific breeding or genetic analysis, and which might mitigate the pressures on existing

major crops (Castañeda-Álvarez et al., 2016; Pironon et al., 2019; Zhang, Li, & Zhu, 2018) if the sociological barriers to their use can be overcome (Morel, Revoyron, San Cristobal, & Baret, 2020).

There is also potential for increased use of fungi. For example, the combination of genomics, DNA synthesis and biotechnological tools available for fermentable fungal species is opening a new era for the production of enzymes and bioactive compounds, and may also help reduce pressure on wild biodiversity (Cairns, Nai, & Meyer, 2018; Deng, Gao, Liao, & Cai, 2017).

2 | TECHNIQUES FOR PLANT IMPROVEMENT

Since the dawn of plant domestication, humans have selected for plants that are well-adapted to growth in the agricultural environment. More recently, farmers and plant breeders have deliberately bred from individuals with desirable traits, leading to the development of elite lines, whose improvement continues to this day. This can be a lengthy process, requiring an initial cross, followed by several cycles of growth, phenotyping, and selection. If an existing elite line is crossed to a less generally well-adapted variety that nonetheless contains certain beneficial genes, the offspring must be repeatedly backcrossed to the elite parent to remove unwanted genetic material derived from the other parent (Lenaerts et al., 2019). Thus, the time taken to introduce a new rice variety to the field is currently 10 years (Acquaah, 2007), and 6–8 generations of inbreeding are required to achieve genetic stability. For slow growing tree species, the time taken to develop a new variety is considerably longer.

2.1 | Impact of genomics on plant breeding

Genomics, the study of the complete genetic composition of an organism, has impacted plant breeding in various ways (Figure 1). An understanding of the molecular basis of biological processes can enable the reengineering of metabolic pathways, to allow for the production of new bioproducts (e.g. synthesis of omega-3 long chain polyunsaturated fatty acids Napier, Olsen, & Tocher, 2019; Ruiz-Lopez, Haslam, Napier, & Sayanova, 2014). Even without mechanistic understanding, the identification of genetic variants (markers) that are statistically associated with desirable traits (due to their close physical proximity in the genome and hence

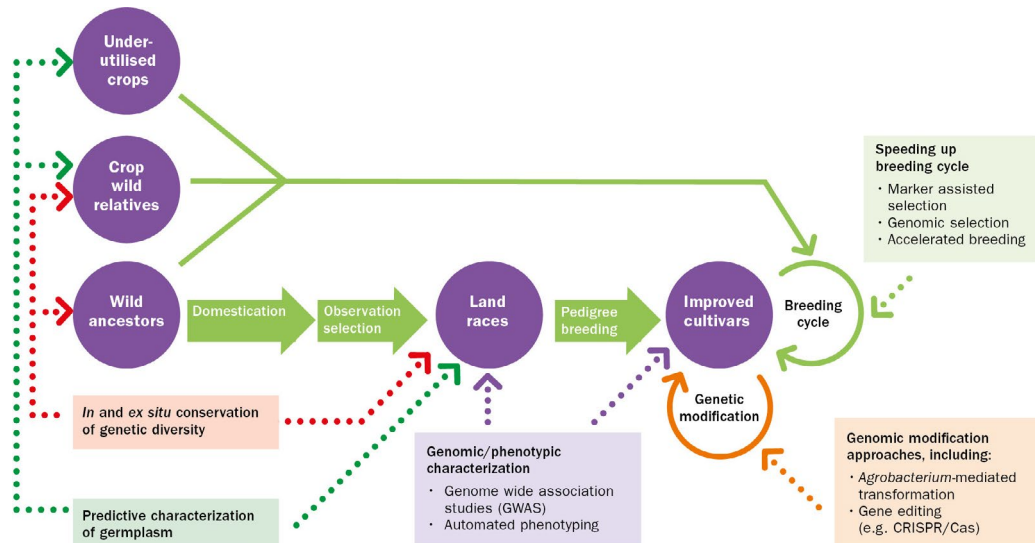


FIGURE 1 Utilization of Plant Genetic Resources for Improving the Useful Properties of Crops. Plant Genetic Resources (plant genetic materials of current or potential value) comprise crop landraces—genetically diverse crop varieties that are the product of traditional seed saving systems not modern plant breeding, commonly associated with local adaptation, and traditional agricultural practices in more marginal agricultural environments (Maxted et al., 2020); Crop Wild Relatives (CWR)—wild species that are relatively closely related to a crop and may be crossed with the crop either using conventional or genetic engineering techniques to introduce desirable traits from the wild species to the crop; and underutilized crops. Traditionally, wild plants have been domesticated and improved through casual selection and pedigree breeding. Modern techniques used to characterize breeding lines include genome size association studies (GWAS) and automated phenotyping. Approaches to accelerate breeding cycles include marker assisted breeding—the identification and use of genetic markers, linked to alleles promoting favorable traits, to identify suitable progeny from crosses at a younger age and lower cost than phenotypically screening mature plants; genomic selection—the statistical prediction of quantitative from a genome-wide scan of genetic variants; and genetic modification—increasingly performed using the CRISPR/Cas technology

likelihood of being co-inherited) allows the prediction of phenotype from genotype. This approach, which is referred to as Marker Assisted Selection (MAS), has been used by breeders since the 1990s (Heffner, Sorrells, & Jannink, 2009) to enable rapid and precise screening for traits of interest at reduced cost (Davey et al. 2011), thereby increasing the speed and precision of the breeding process. Tracking the presence of specific genetic variants also allows for gene stacking, that is, the incorporation of multiple genes independently conferring a single trait, such as disease resistance. For example, plant pathogens often evolve the ability to overcome resistance conferred by a single gene following the widespread planting of resistant crops. Stacking multiple resistance genes within the genome increases the durability of the trait (e.g. wheat resistant to rust fungi has been bred using this approach, Ellis, Lagudah, Spielmeier, & Dodds, 2014). Another potential use is the development of more efficient biofuels: research has shown the potential of using gene stacking to incorporate several biosynthetic genes which increase the percentage of easily fermentable biosugars while reducing the lignin content of plants without restricting overall growth (Aznar et al., 2018), although yield in the field remains difficult to predict.

Genomic Selection (GS) utilizes a high-density of markers from across the whole genome to statistically predict polygenic traits such as yield, reducing the reliance on finding significant associations with genes of large effect (Meuwissen, Hayes, & Goddard, 2001; Wang,

Xu, Hu, & Xu, 2018). As with MAS, it is not necessary to understand the molecular mechanisms behind a complex trait to carry out genomic selection, as long as the phenotypic variation is highly heritable, and samples are adequately genotyped and phenotyped. Models are developed using a training population in which the genotype and phenotype for the trait is known for each individual, using the combined effects of all markers to predict the genomic breeding value (i.e. the heritable component of the trait) in individuals outside the training set. Improvements to the trait are obtained by increasing the frequency of favorable alleles in the population or line over many generations. Genomic selection methods have been less widely adopted for plant than animal breeding (Hickey et al., 2017), but nonetheless they are increasingly being used in some major crops (e.g. soya, maize, wheat and cotton) to increase yields and disease resistance, and hence improve crop quality (Crossa et al., 2017; González-Camacho et al., 2018; Michel et al., 2018; Rutkoski et al., 2015), while proof of concept has also been demonstrated for quality traits, such as the baking qualities of bread wheat (Michel et al., 2018). In the staple food crop cassava, in which phenotypic selection alone is inefficient and heritability of desired traits is low, genomic selection has been shown to accurately predict yield traits in multiple trials (de Andrade, Sousa, Oliveira, Resende, & Azevedo, 2019). Nevertheless, the presence of polyploidy and high heterozygosity in many crop genomes is currently limiting the widespread application of genomic selection (Friedmann et al., 2018).

In long-lived species such as forest trees, the potential advantages of genomic selection are perhaps even greater, especially in combination with speed breeding approaches that can considerably shorten the generation time of a crop (Hickey et al., 2019). However, its use has been limited by the prohibitive costs of obtaining the necessary training datasets (Hickey et al., 2017). Recently, methods such as the sequencing of pools of individuals with similar phenotypes (e.g. ash trees (*Fraxinus excelsior*) resistant to ash dieback, Stocks et al., 2019) have been shown to reduce costs and hence may enable the extension of genomic selection to such species.

2.2 | Conventional transgenic approaches

A more radical way to decrease breeding times is through the direct genetic modification (GM) of an individual, enabling the introduction of a desired gene (potentially sourced from an unrelated species) into an elite line without introducing unwanted genetic material. A typical approach is to use a plant pathogen, *Agrobacterium*, to carry the desired genetic material into a plant (Alok, Sharma, Kumar, Verma, & Sood, 2017). A common application of this approach has been to enrich the nutrient content of edible crops. For example, transgenes have been used to increase the uptake or synthesis of vitamin A, iron, and zinc in crops including rice, wheat, maize, and cassava (Kumar, Palve, Joshi, Srivastava, & Rukhsar., 2019); folate in rice; Omega-3 in oil seed rape (canola), and ascorbate in maize (Chen & Lin, 2013). Toxin-encoding genes from the bacterium *Bacillus thuringiensis* (Bt) have also been inserted to generate resistance to insect pests in multiple crop species including cotton, maize, and aubergine (Abbas, 2018; Prodhan et al., 2018); and multiple Bt proteins have been stacked with no new evident risks to non-target insects (Romeis & Meissle, 2020). As of 2016, 185.1 million hectares or about 12% of global cropland (54% in low-income countries) have been planted with GM crops (Pellegrino, Bedini, Nuti, & Ercoli, 2018). Consumption of GM foods is generally considered safe (Nicolia, Manzo, Veronesi, & Rosellini, 2014; Ronald, 2011) with no greater risks than conventional food (Directorate-General for Research and Innovation (European Commission), 2010; National Academies of Sciences Engineering & Medicine, 2016), and GM crops have generally shown increased yields and reduced pesticide usage (Ahmad & Mukhtar, 2017; Klümper & Qaim, 2014).

The merits of transgenic technology, however, are partially overshadowed by its perceived harm to the environment. One issue is the possible transfer of the transgene to crop wild relatives by natural pollination (transgene escape) (Ahmad & Mukhtar, 2017; Arias & Rieseberg, 1994; Gilbert, 2013), or through the intermixing of GM and non-GM seeds via seed sharing between farmers (van Heerwaarden, Ortega Del Vecchio, Alvarez-Buylla, & Bellon, 2012). Long-term monitoring of transgenes to study their impact on local ecology is currently limited, although recent studies highlight how the risks associated with any transgene need to be assessed separately for each GM modified species since the ecological impact is

Box 1 Engineering herbicide resistance in tomato and watermelon by CRISPR/Cas genome editing

A modified version of Cas9, an enzyme involved in bacterial immune responses (Deltcheva et al., 2011), can be used to directly alter genomic DNA to match an RNA template carrying a desirable alteration with high fidelity and efficiency (Komor, Kim, Packer, Zuris, & Liu, 2016). Acetolactate synthase (ALS) is an enzyme involved in plant amino acid biosynthesis and is commonly targeted by herbicides, which inhibit its active site (Lonhienne et al., 2018). Mutated forms of the ALS gene encoding this enzyme confer resistance to herbicides but it was difficult to breed into some crops by conventional means. By using a modified version of Cas9, researchers have been able to introduce single nucleotide changes into the ALS genes of tomato (Shimatani et al., 2017) and watermelon (Tian et al., 2018), conferring heritable herbicide tolerance with no evidence that any off-target modifications have been introduced. The speed and precision of this approach has revolutionary potential for future crop improvement.

likely to be influenced by the biology of the crop, wild species, and transgene (Ellstrand, 2018).

2.3 | Precision genome editing approaches

An alternative to conventional transgenic methods is the use of sequence-specific nucleases to perform targeted manipulation of precise locations within the genome to create desirable genetic variants in situ (Chen, Wang, et al., 2019; Hua et al., 2019). Zinc finger nucleases (ZFNs) and transcription activator-like effector nucleases (TALENs) have been applied to various crops to modify traits such as herbicide tolerance or disease resistance (Zhang, Massel, Godwin, & Gao, 2018), but currently the most efficient, flexible, and cheapest approach is the use of clustered regularly interspaced short palindromic repeats (CRISPR) to guide editing by CRISPR-associated (Cas) enzymes (Zhang, Malzahn, Sretenovic, & Qi, 2019; Zhang, Massel, et al., 2018). CRISPR/Cas has been used to generate a range of modifications within the genome, including knockouts (to disrupt gene function), insertions/replacements (to introduce new alleles or alter gene expression patterns), and base editing (to modify traits controlled by single nucleotide variants or to alter RNA splicing) (Chen, Wang, et al., 2019; Zhang, Massel, et al., 2018). The precision and speed of these approaches has transformational promise for crop improvement (Jaganathan, Ramasamy, Sellamuthu, Jayabalan, & Venkataraman, 2018). They have already been applied to food and other crops to improve a range of different traits, including yield, quality (e.g. nutritional composition, digestibility, shelf-life), disease, insect and herbicide resistance, cold and drought tolerance, and

nitrogen use efficiency (Chen, Wang, et al., 2019; Hu et al., 2015; Shimatani et al., 2017; Zhang, Massel, et al., 2018); a specific example in watermelon and tomato is discussed in Box 1. Moreover, the ability to alter multiple genes simultaneously via multiplex editing and gene stacking (see above) is contributing to efforts to improve complex quantitative traits such as durable disease resistance (Nelson, Wiesner-Hanks, Wisser, & Balint-Kurti, 2018) and yield (Chen, Wang, et al., 2019; Hua et al., 2019).

While initially this technology was mainly used in major crops, it is now being applied to minor crops as well. For example, orthologues of genes known to be involved in tomato domestication and improvement have been modified to enhance productivity traits in groundcherry (*Physalis pruinosa*) (Lemmon et al., 2018). Meanwhile, a vigorous public debate between different countries is occurring about the correct regulatory approach for CRISPR-modified crops. European Union legislation treats single nucleotide edits comparably to the introduction of foreign DNA (Eriksson et al., 2020), resulting in reduced levels of patent filing compared with other parts of the world (Martin-Laffon, Kuntz, & Ricroch, 2019).

3 | ADVANCES IN IMPROVING THE USEFUL PROPERTIES OF FUNGI

Fungi are used by humans for their intrinsic properties (e.g. as food, medicines), as chassis for the production of endogenous and exogenous biomolecules, and as transformational agents in processes such as bread, alcohol, and cheese production (Prescott et al., 2018). Fungi with useful traits were initially stochastically selected from wild diversity, as the complex fungal life cycles and sexual incompatibilities were obstacles to deliberate breeding. For example, breeding the widely cultivated edible mushroom, *Agaricus bisporus*, was impossible before the discovery of new strains with compatible breeding types in the late 1970s (Fritsche, 1983). Since then many hybrids have been bred and are being tested for their ability to make new forms of beer and biofuels (Alexander et al., 2016; Savoie, Foulongne-Oriol, Barroso, & Callac, 2013; Singh, Shwet, & Sharma, 2017).

In the last 15 years sequencing of fungal genomes and the development of bioinformatics tools to predict biosynthetic pathways has improved our understanding of how the production of fungal secondary metabolites is regulated. This has increased our ability to produce fungal bioactive compounds (Nielsen et al., 2017), and driven new approaches for screening fungi for new useful products. For example, molecules that modify chromatin confirmation are now commonly used to induce expression of otherwise “silent” biosynthetic pathways leading to the production of previously unknown secondary metabolites (Collemare & Seidl, 2019; Henrikson, Hoover, Joyner, & Cichewicz, 2009; Pfannenstiel & Keller, 2019). Alternatively, the OSMAC (one strain many compounds) framework uses multiple growth conditions to yield new compounds (Romano, Jackson, Patry, & Dobson, 2018). The ecological roles of fungal secondary metabolites in microbial communities are also increasingly used to induce

production of novel compounds (Knowles et al., 2019; Nielsen et al., 2017). For example, bacteria-fungi and fungi-fungi co-cultivation often yields new compounds with important antimicrobial properties, as recently shown for lagopodin B produced by *Coprinospin cinerea* in the presence of bacteria (Stöckli et al., 2019), and for berkeleylactones produced when two extremophile *Penicillium* species were grown together (Stierle et al., 2017). However, such interactions may be restricted to specific bacterial and fungal species (e.g. Schroeckh et al., 2009), and hence this approach may prove difficult to implement in high-throughput platforms.

4 | INCREASING THE POOL OF GENETIC DIVERSITY TO EXPAND OPPORTUNITIES FOR INCORPORATING USEFUL TRAITS IN SOCIO-ECONOMICALLY IMPORTANT PLANTS AND FUNGI

The approaches discussed above have improved the usefulness of plants and fungi to humans, but often at the price of narrowing their genetic diversity, making them more vulnerable to pests, diseases, and unpredictable climates. This recognition has led to the search for additional sources of genetic diversity that have the potential to enhance productivity, sustainability, and resilience of crops. Such genetically diverse materials may be directly bred into commercial lines or used for information and inspiration when designing custom genetic modifications.

For plants, much work has focused on the identification, conservation, and curation of plant genetic resources (PGR, defined as “genetic material of current and potential value”, CBD, 1992). Of the diversity of PGRs that have been recognized (Maxted, Hunter, & Ortiz Rios, 2020), the ones that contain the greatest wealth of genetic diversity for breeding are the crop landraces and crop wild relatives (CWR). Many CWR already possess potentially useful traits, such as resilience to disease, drought, or salinity (Zhang, Li, et al., 2018). There are two broad conservation strategies, each comprising a range of techniques to conserve plant genetic diversity (and defined by the CBD (2002): (1) *in situ* conservation of ecosystems and natural habitats and the maintenance and recovery of viable populations of species in their natural surroundings, and, in the case of domesticated or cultivated species, in the surroundings where they have developed their distinctive properties; and (2) *ex situ* conservation of components of biological diversity outside their natural habitats – especially in seed banks, such as those maintained by CGIAR (Byerlee & Dubin, 2009), the Svalbard Global Seed Vault (Westengen, Jeppson, & Guarino, 2013), and Kew's Millennium Seed Bank for wild plant species (Liu, Breman, Cossu, & Kenney, 2018).

In the long-term, maintaining diversity *in situ* is fundamental to supporting food security (Dulloo, 2019). Conserving landraces and CWRs on-farm or in the wild allows the plants to adapt and evolve in their own niche environments and develop unique properties that make them major providers of genetic materials for use by breeders and farmers. Although CWR diversity is found in numerous

protected areas, CWRs per se are rarely actively conserved (i.e. the populations are not actively managed to maximize the maintenance of genetic diversity) or made available to users. A more systematic, complementary approach to PGR conservation that includes active *in situ*/on-farm conservation has the potential to more than double the genetic diversity available to breeders and farmers for crop improvement (Dulloo, 2011; Maxted et al., 2020).

Initiatives such as “Adapting Agriculture to Climate Change” (Dempewolf et al., 2014) have helped plug gaps in *ex situ* CWR collections, and ensure that seed material is curated and stored appropriately to safeguard its long-term viability. However, it is estimated that 8%–20% of angiosperm species produce desiccation-sensitive seeds that are recalcitrant to “standard” seed banking methods (Wyse & Dickie, 2017), hence alternative approaches such as cryopreservation (Li & Pritchard, 2009) and pollen storage are being developed. Overall, it is recommended that a combination of *in situ* and *ex situ* techniques are applied to each species to provide backup if one method fails (Dulloo et al., 2017).

CWRs and landraces often lack the necessary characterization and evaluation (C&E) data needed for their systematic utilization in breeding programs (Dempewolf et al., 2017; FAO, 2017). Nevertheless, predictive characterization approaches that combine geospatial analyses together with environmental and agro-ecological data can support the selection of candidate accessions that are suitable for investigating a specific trait from uncharacterized germplasm (Thormann et al., 2016). They build on the hypothesis that different environments exert divergent selective pressures on plant populations, and thus populations growing in a specific environment will possess a suite of adaptive traits shaped by selection pressures unique to these environments. The potential for a trait to be present is enhanced by (1) matching of biotic and abiotic characteristics associated with a collection site; (2) ecogeographical information associated with a collection site; and (3) previously records of trait occurrence associated with a set of locations different from those where the germplasm being examined has been collected or observed. In each case a predictor is used to build a hypothesis that germplasm from a particular location will be genetically differentiated. One of the first systematic applications of this approach, the Focused Identification of Germplasm Strategy (FIGS) (Mackay & Street, 2004; Street et al., 2008), applied the biotic and abiotic matching techniques mainly to major crops. Building on this, more recent studies using ecogeographical information or previously recorded C&E data have been developed and tested for their applicability to CWR (Thormann, 2012), exploring the so-called ecogeographical filtering and calibration methods (Thormann et al., 2014; Thormann et al., 2016). Although predictive characterization does not replace actual field trials, it considerably reduces the size of the trial required by reducing the set of candidate accessions which need to be screened before finding novel alleles for target traits; it has been used successfully in several species including barley (Endresen, 2010) and white clover (García Sánchez, Parra-Quijano, Greene, & Iriondo, 2019).

5 | FUTURE DEVELOPMENTS

Many of the technologies discussed above are still relatively new but have the potential for further development. For example, advances in DNA synthesis and heterologous expression systems (Skellam, 2019) are providing new opportunities to explore fungal biodiversity for novel bioactive compounds and use fungi to produce them. The number of known fungal pathways remains limited with only 277 biosynthetic pathways characterized compared to 1,611 bacterial ones (Kautsar et al., 2019). There is a clear need to further characterize fungal biosynthetic genes and link them to the fungal chemical landscape. In particular, bioinformatics tools dedicated to fungal genomes are needed to efficiently and accurately mine genomes.

Large-scale genomic studies are also needed to prioritize functional studies and avoid studying already characterized biosynthetic pathways (Bushley & Turgeon, 2010; Chooi & Tang, 2012; Navarro-Muñoz & Collemare, 2020). With increased numbers of characterized pathways, we may be able to produce new-to-nature natural products, such as biosynthetic enzymes engineered to perform chemical reactions that are difficult to obtain synthetically due to their specificity (Fürtges, Obermaier, Thiele, Foegen, & Müller, 2019), or produce higher yields of potentially useful compounds (Rebets, Brötz, Tokovenko, & Luzhetskyy, 2014). For example, the combination of biosynthetic genes from the autinoid pathway in *Aspergillus nidulans* and *A. calidoustus* (Valiante et al., 2017) has redirected the pathway toward the production of the insecticide calidodehydroaustin in the fermentable *A. nidulans* strain (Mattern, Valiante, Horn, Petzke, & Brakhage, 2017). Chimeric enzymes and combinatorial expression of biosynthetic genes can also result in novel derivatives of known compounds as shown for fungal macrolide lactones with potential anti-tumor, anti-malarial, and anti-bacterial activities (Xu, Jiang, Zhang, Ma, & Guo, 2014a; Xu, Zhou, et al., 2014) and fungal cyclodepsipeptides with novel antiparasitic activity to treat, for example, the potentially fatal Chagas disease and Leishmaniasis (Steiniger et al., 2017). Indeed, combining genes from different pathways is a very promising approach to increase the diversity of chemicals produced by fungi (Frandsen et al., 2018; Li et al., 2018). Yet although scalable platforms for heterologous expression in fungal strains are becoming available (Harvey et al., 2018), optimization is needed to consistently reach high production levels. This will require not only improvement of the primary metabolism as already performed but also better coordination of the expression of biosynthetic genes and improved metabolic fluxes through better compartmentalization of biosynthetic steps.

While the use of genome editing tools such as the CRISPR/Cas systems have great promise for improving traits in plants and fungi, there are still challenges arising, for example, from the low frequency of successful gene editing in somatic cells and the precision with which the desired modifications in the DNA sequences are achieved. Nevertheless, advances are continually being made, improving precision and efficiency (Bharat, Li, Li, Yan, & Xia, 2019; Hu et al., 2015; Hua et al., 2019; Kang et al., 2018; Shan & Voytas, 2018; Shimatani et al., 2017). Recent developments in the

genome editing repertoire include (1) the development of novel RNA editing systems (Anzalone et al., 2019; Bharat et al., 2019) (although the application of these in plants has yet to be realized); (2) the genetic engineering of the Cas9 enzyme to extend the range of target sites that can be edited (Niu et al., 2020); and (3) novel approaches that can achieve spatial (e.g. cell-, tissue- or organ-specific) and/or temporally localized modified genes by including tissue- or cell-specific promoters (e.g. CRISPR/TSKO (Tissue Specific Knock Out), Decaestecker et al., 2019; Ali, Mahfouz, & Mansoor, 2020). Examples of potential applications being pursued include the development of more efficient biofuel crops. To achieve this the aim is to restrict the expression of genes involved in lignin production to xylem vessels where it is essential, while reducing lignin content in fibre cells (Liang et al., 2019) where it can decrease the efficiency of converting plant mass into energy. The recent identification of unique genomic characteristics of the way that CRISPR/Cas9 operates in filamentous fungi (Yamato et al., 2019), which are widely used in the bioprocessing, food, and fermentation industries, is likely to facilitate more flexible genome editing in these organisms as well.

In addition to breeding techniques that focus directly on genetic material, other approaches currently in development include selection for stable epigenetic modifications (Gallusci et al., 2017), utilizing the microbiome of plants to increase their resilience (Carrión et al., 2019), and the production of hybrids at commercial scale for self-pollinating species (such as wheat) through the genetic modification of genes controlling fertility (Gupta et al., 2019).

There is the further potential to combine genome editing techniques with synthetic biology approaches to introduce traits that are entirely novel to a given species. For example, nitrogen-fixing capabilities could be extended to new plant species by using CRISPR/Cas systems to insert synthetic DNA sequences (genes or regulatory elements) into their genomes (Chen, Wang, et al., 2019), reducing the need for artificially fixed nitrogen (Wurtzel et al., 2019), while the efficiency of the photosynthetic cycle could be increased in common cereal crops by changing the pathway for carbon fixation (Ermakova, Danila, Furbank, & von Caemmerer, 2020). However, there are broad biological constraints upon these processes beyond the enzymatic repertoire, and these goals are unlikely to be realized in the near future. The use of genome editing for the *de novo* domestication of wild plants as potential novel crops has also been highlighted, and species that might be good candidates for such an approach have been proposed (Fernie & Yan, 2019).

A recent report from the World Resources Institute concluded that “the case for using [genetic engineering] is compelling when the full range of potential gains and costs is taken into consideration” (Searchinger et al., 2019). Nonetheless, public perception of GM crops remains poor in many countries, with limited scientific understanding amongst many of the public and the perception that GM crops are “unnatural” and therefore unsafe (Babar et al., 2020; McFadden & Smyth, 2019; McPhetres, Rutjens, Weinstein, & Brisson, 2019). Interestingly, conventional breeding in sweet potato

has selected for genes introduced to the species by *Agrobacterium* in the wild (Kyndt et al., 2015), similarly to the way GM is performed in the laboratory, and overall, the evidence clearly suggests that the risk to the environment of a new variety should be considered primarily in light of its phenotype and not in the methodological approach used to produce it (National Academies of Sciences Engineering Medicine, 2016). However, in some jurisdictions, the regulatory environment does not reflect the scientific consensus. For example, European Community law is heavily process-focused and is much more restrictive of the use of genetic modification than of untargeted mutagenesis (Anzalone et al., 2019; Callaway, 2018). An evidence-based regulatory approach is essential if the potential benefits of these technologies are to be realized.

Even with the use of genomic approaches, phenotyping is still necessary when exploring biological mechanisms, identifying marker loci, and confirming that the desired phenotype is achieved at the end of the process. Recent advances in automated phenotyping (which enable rapid and accurate screening of large numbers of plants) include remote sensing (at various scales), and the development of automated greenhouses and large growth chambers with sophisticated climate control (Zhao et al., 2019). A common characteristic of these novel approaches is that they are extremely data-generative, leading to a growing interest in machine-learning techniques to assess and interpret their outputs (Mochida et al., 2018; Taghavi Namin, Esmailzadeh, Najafi, Brown, & Borevitz, 2018; Ziamtsov & Navlakha, 2019). One example is the phenotyping of root traits (e.g. quantifying root growth), which have historically been difficult to observe under realistic conditions (Chen, Palta, Wu, & Siddique, 2019). Until recently this had been achieved by “shovelomics”, i.e. digging root systems out of the soil and visually assessing them (Trachsel, Kaeppler, Brown, & Lynch, 2011). The novel methods of phenotyping plant roots now being developed are likely to accelerate the improvement of root traits and their inclusion in plant breeding programmes (Tracy et al., 2020).

We can also expect a continued fall in the cost of genome sequencing, leading to the increased availability of high-quality reference genomes (e.g. of currently utilized plants and fungi, and their relatives), and large scale low coverage sequencing of, for example, progeny in breeding programmes, cultivars, landraces, CWRs, and wild populations. In seed and fungal biobanks, it is likely that an increasing proportion of all material will be sequenced, establishing the relatedness between individuals (Singh et al., 2019) and the completeness of collections (Milner et al., 2019). This will enable the most appropriate material to be selected for novel phenotypic screening programmes and breeding schemes. DivSeek (<https://divseekintl.org/>), a global initiative bringing together most of the world's largest seed banks, aims to develop standards for the generation and curation of genotypic and phenotypic information and provide the link between plant breeders and public germplasm collections. The obstacles to delivering this vision are as much sociological as they are technical, including the linkage of access to genetic material (and derived information) to benefit sharing, and are being discussed in the context of the Convention on Biological Diversity (CBD), amongst

other forums (Williams et al., 2020). The failure to deliver expected direct economic benefits from the use of biodiversity to date may be due to defects in the model explicit in the CBD (whereby biodiversity conservation is effectively expected to pay for itself) (Laird et al., 2020) as well as in its implementation. Nonetheless, if these difficulties can be overcome, there is great potential for further utilizing the global genetic diversity to advance the common good.

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AUTHOR CONTRIBUTIONS

P.J.K. and I.J.L. conceived and edited the manuscript. All authors contributed to writing and reviewing the manuscript.

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