Trends of Biotechnology Applications in Pest Management: A Review

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Abstract
There are many constraints that severely affect the global agricultural production and productivity which include the ever increasing of population growth, degradation of natural resources, climate changes and emerging pests. Among these factors, biotic constraints or pests are known to cause 25-50% or complete loss of plant production. Accordingly, various plant protection technologies have been deployed with the trend of focusing on the use modern biotechnological tools that are proven to be most effective and mandatory. The review covers a wide array of pest management methods ranging from the conventional biological control methods up to molecular breeding techniques. Furthermore, the application of new genetic engineering techniques fueled by new breakthroughs and innovations are the cornerstone of this review. Accordingly, the continuous increasing trend of GM crops cultivation in both crop type and hectare has urged many countries to deploy the technology as a key strategy to enhance their bioeconomy. In fact, plant protection is the discipline that immensely benefit from biotechnology than any other disciplines for ensuring food security and sustainable development. However, in order to fully exploit the enormous potential of biotechnology, appropriate biosafety regulatory frameworks and proper stewardship programs need to be effectively implemented. This integrated approach can promptly help respond to the ever-dynamic threat of pests and hence reliably combat food insecurity and ably contribute to sustainable development.

Keywords: pest management; bio-agents; molecular breeding; genetic engineering; GM Crops production trend; Genome editing

Role of Plant Protection for Improving Agricultural Production and Productivity
According to The Food and Agriculture Organization of the United Nations (FAO) 2017 report “The future of food and agriculture: trends and challenges”, the world's population is expected to increase by 2 billion persons in the next 30 years, from 7.7 billion currently to 10 billion in 2050. To this effect, food production must double by 2050 to meet the demand of the world’s growing population and innovative strategies are needed to help combat hunger, which already affects more than 1 billion people in the world. On the other hand, human population growth is seen as the main cause of other biologically and ecologically destructive phenomena (Hopfenberg and Pimentel, 2001). FAO (2017) report identifies 15 trends and 10 challenges affecting the world's food systems which will have to be addressed in order for sustainable agricultural services to meet the growing food demand of the world population.
Subsequently, Calicioglu et al., (2019) analyzed these future challenges of the agriculture and food systems by focusing on (i) their root causes and trends; and (ii) the inter linkages among the solutions proposed to address the challenges, in which transboundary pests and diseases are described as one of the root cause of challenges.

To this end, the ever increasing of population growth together with the inevitable degradation of natural resources, climate changes and emerging pests are the major constraints that severely affect the trend of global agricultural production and productivity. Among these production challenges and constraints, abiotic factors [temperature (chilling/frost or heat), water (drought or flooding) and salts (high salinity or mineral deficiency)] and biotic or biological factors (pests) are responsible for reduction of crop performance and resulting in a lower actual yield than attainable production of crops (Oerke, 2006). In some instances pests remain to be one of the major limiting factors in sustaining the productivity of agriculture. Interestingly these biological factors (pests) can be prevented, controlled and managed there by deploying appropriate plant protection measures. To tackle these challenges, there is a pressing need to evolve towards more sustainable and modern agricultural practices that can revolutionize the bioeconomy.

Under the International Plant Protection Convention, a pest is defined as any species, strain, or biotype of plant, animal, or pathogenic agent injurious to plants or plant products (ISPM, 2006). Accordingly, unless otherwise stated, throughout this article the term “pests” refers to plant pathogenic microorganisms (bacteria/mycoplasma, fungi, viruses, nematodes), insects (arthropods or entomophagus/herbivorous/ phytophagous arthropods and mites) and weeds (parasitic higher plants), that affect the growth of plants and consequently reduce the yields and qualities. In general plant protection research deals with five sequential interventions or thematic areas namely (i) survey and surveillance on the distribution, severity, prevalence etc of pests, (ii) detection, diagnosis, identification and characterization of pests, (iii) basic studies on the biology and epidemiology of pests (iv) determine the losses they incur in terms of quality parameters and quantity or yield components and (v) develop control measures or management options (cultural or mechanical, chemical, biological, host plant resistance and integration of two of these or more measures to attain holistic integrated pest management (IPM). In all of these sequential steps, the role of biotechnology is very critical and mandatory.

Plants account for over 80% of the human diet. Depending on the plant and prevailing environment, pests are estimated to be responsible for 25 to 50% or complete loss of agricultural production and productivity (Oerke, 2006; Savary et al., 2012; CAST, 2017). This clearly indicates that pests pose serious threats to food security and sustainable development. This calls for devising effective plant protection technologies for the prevention and control of crop losses due to pests in the field (pre-harvest losses) and during storage (post-harvest losses) (Oerke, 2006). In fact, effective pest management requires enhanced skills and most costly inputs due the complex interaction of pests with environment and weather factors or climate changes (Juroszek and Von Tiedemann 2013). This is due to the fact that these pests are difficult to control as their populations are variable in time, space, and genotypes and new aggressive strains are likely to occur leading to outbreaks, invasiveness and global spread. These dynamic complexities of pests urge the deployment of deployment of series of reliable plant protection measures ranging from conventional up to modern biotechnology products so as to curb new outbreaks and associated causal factors. Apparently, the sustainable use of effective plant protection measures by itself incredibly contribute to the enhancement of agriculture production and productivity. Thus, plant protection has an obvious role to play in meeting the growing demand for food security and sustainable development (Savary et al., 2012).

There are several publishers that produce articles on plant protection. Among these, Lebeda et al. (2014) reviewed the 50 years (1965–2014) of publication of plant protection science and indicate the advancements made progressively. The review of crop protection contributions toward agricultural productivity can also be found from CAST (2017) which was produced as part of the series on the need for agricultural innovation to sustainably feed the World by 2050. To this end, the present review aimed at enhancing these efforts thereby focusing on the application of biotechnology to plant protection, particularly to pest management aspect to ensure food security and sustainable development.

Role of Biotechnology in Plant Protection and Agriculture

According to the Convention on Biological Diversity (CBD, 1992), the term ‘biotechnology’ means “any technological application that uses biological systems, living organisms, or derivatives thereof, to make or modify products or processes for specific use.” Biotechnology can be considered as a series of enabling technologies, which each involve the elucidation and manipulation of living organisms (plants and pests) or their subcellular components to develop useful products, processes and services (Lebeda and Pokorný, 2012; Cano et al., 2017). The technologies are among the most exciting, cutting-edge applications of contemporary biological sciences which include DNA based characterization of plants and pests, plant tissue and cell cultures, monoclonal antibody production, molecular breeding techniques, recombinant DNA technology and/or genetic engineering, bioprocess
engineering, and bioinformatics (Fermin-Munoz et al., 2000; Gianessi et al., 2003).

**Biotechnology in Plant Protection**

Biotechnology application in plant protection can also be broadly divided in to two categories namely (i) characterization of pests and (ii) management of pests. The first application has made significant advances in the rapid and accurate diagnosis of pests and genetic characterization of their populations. This part of biotechnology application is treated separately elsewhere. This first application is found to be so a crucial prerequisite to devise reliable pest management strategies as it enables identification of resistant markers for plants as well as DNA regions of the pests associated with resistance which ultimately speed-up the breeding of cultivars having various traits.

The second part of the application is the subject of this review article and deals with both conventional and modern biotechnological pest management strategies, in which the latter is the current trend which include molecular breeding and genetic engineering techniques. Various reviews describe the application of these biotechnological methods used in pest management (Gianessi et al., 2003; Wahab, 2009; Duke 2011). There are also several reviews separately treated for diseases, insect-pests and weeds. Some of them are biotechnology for disease management (Fagwalawa et al., 2013; Shamim et al., 2013; Vincelli, 2016; Arya 2018; Dayou et al., 2018); biotechnology for insect-pest management (DeVilliersand Hoisington, 2011; Stevens et al., 2012; Talukdar, 2013; Jaiswal et al., 2018) and biotechnology for weed management (Tranel and Horvath, 2009; Duke et al., 2015; Westwood et al., 2018). It can be clearly seen that plant protection is the discipline that immensely benefit from biotechnology in many ways than any other disciplines.

**Biotechnology for Improving Agricultural Production and Productivity**

There are two series of agricultural technology developments that have been practiced namely “Green Revolution” (1944-1994) and “Gene Revolution” as of 1995 up until now (Ghanian et al., 2016; Ameen and Raza, 2017). The “Green Revolution” focused on extensive use of agrochemicals (chemical fertilizers, pesticides and herbicides), heavy machinery and irrigation infrastructure. In addition to these, high-yielding crop varieties (hybrid cereals) developed through conventional plant breeding practices were also used and resulted in the increased crop productivity in some countries. However, the ever-rising global population growth demanded equivalent amount of food production, for which the conventional plant breeding alone, can no longer respond. Thus it was replaced by “Gene Revolution” which is also referred as the era of modern biotechnology that eliminated the barriers of traditional methods of plant breeding through genetic engineering techniques (Ghanian et al., 2016).

Actually, biotechnology in agriculture is not only about genetic modification but rather encompasses a number of tools and elements of conventional breeding techniques, bioinformatics, microbiology, molecular genetics, biochemistry, plant physiology and molecular biology. The advances made in cell biology and cellular genetics have resulted with breakthroughs in biotechnology that revolutionized agricultural production for developing plant varieties containing several beneficial characteristics including traits that confer resistance to biotic and abiotic factors. Gene technology identifies desirable traits more quickly and accurately than conventional plant breeding. It can also introduce the genes that control desirable traits into plants with far greater precision and control than conventional methods. The applications of biotechnology in crop improvement and agriculture were reviewed by several scholars (Herdt 2006; Dunwell 2010; Gosal et al., 2010; Sharma et al. 2012; Nasser 2014; Khan et al., 2018).

**Biotechnology for Pest Management**

The application of biotechnology in pest management can be broadly divided into two categories namely (i) conventional biotechnology and (ii) modern biotechnology. This review article appears to be unique as it covers the exhaustive and comprehensive application of these two broad categories of biotechnology in pest management. The application ranges from the pioneer conventional management measures (non-transgenic or that do not involve gene transfer) to the ultimate aim of describing the most powerful and modern biotechnological pest management options that dwell on molecular breeding and genetic engineering techniques. Each of the application is referenced across the three pests (diseases, insects and weeds) in a matrix form that ultimately update previous separate reviews and hence aid simultaneous understanding of application for enhanced deployment strategy.

**Conventional Biotechnology Products Used in Pest Management**

The conventional biotechnology products or the non-transgenic technologies used for the control of pests involve the whole range of bio-agents, tissue culture techniques and biofertilizers.

### 1. Bio-Agents Used for Pest Management:

Bio-agents are all sort of biological agents consisting of microbial agents, natural enemies, parasitoids and parasites; and botanicals. Several types of biocontrol agents (Barratt et al., 2018) and biopesticides (Cavoski et al., 2011), which are broadly used interchangeably have been used as conventional biotechnology products for the management of pests. These pest control agents are composed of either of the bio-agents (Guleria and Tiku, 2009; Cavoski et al., 2011; Enyiukwu et al., 2016) and their Secondary metabolites (Mazid et al., 2011; Pino et al., 2013). These components can be used alone or combined with each other.
to sustainably maximize the benefits (Barzman et al., 2015; Stenberg, 2017).

2. Integrated Pest Management (IPM) Strategies
The above-mentioned biological control measures can be more sustainable when combined with each other and enjoyed immense application in devising effective and holistic approach of Integrated Pest Management (IPM) strategies to sustain agricultural production (Nafiu et al., 2014). IPM is an ecologically-based pest management strategy that incorporates all appropriate methods into a systematic approach to minimize pest damage. It is globally endorsed as the future paradigm and advocate the integration of six components namely (i) biological control, (ii) host plant resistance, (iii) cultural control, (iv) mechanical and physical control, (v) chemical control and (vi) regulatory control. IPM emphasizes the growth of healthy plant with the least possible disruption to agro-ecosystems and encourages natural pest control mechanisms (Barzman et al., 2015; Stenberg, 2017; Dara 2019).

3. Tissue Culture Techniques
In addition to these, mass production of disease-free planting materials using plant tissue culture techniques are revolutionizing the pest management strategies dealing with host plant resistance. Tissue culture (TC) methods facilitates rapid multiplication of disease-free plants under controlled and aseptic conditions in a relatively short time. Itoffer a rich scope for creation, conservation, and utilization of genetic variability for the improvement of plants (Sharma et al., 2012; Gaikwad et al., 2017). Tissue culture techniques have been used for mass multiplication of plants and their conservation (Gosal et al., 2010; Hussain, et al., 2012; El Meskaoui, 2013; Ghaffar et al., 2016; Rashid et al., 2017; Oseni et al., 2018). These in vitro techniques (TC) also enjoyed enormous application for the production of secondary metabolites (Namdeo 2007; El Meskaoui, 2013). Furthermore, TC are also applied for in vitro screening for disease resistant plants (Rai et al., 2011; XiaoXing et al., 2013; Gao and Sun, 2013; Kumari et al., 2014).

Similarly, haploid technology and protocols are used for production of haploids and double haploids of homozygous plants which significantly impacted the agricultural systems. Nowadays, these biotechnologies represent an integral part of the breeding programmes of many agronomically important crops (Mishra et al., 2015; Begheyn et al., 2016; Badu et al., 2017; Ren et al., 2017).

4. Biofertilizers
The fertility of the plant growing medium (soil) need to be maintained for the plants to thrive and grow healthy and ably augment the plant protection measures. In this regard microbial biotechnology products such as biofertilizers [Biological Nitrogen Fixing (BNF), Phosphate Solubilizing Bacteria (PSB), Potassium Mobilizing Bacteria (KMB), Plant Growth Promoting Bacteria (PGPB), Mycorrhiza] have been used improving soil fertility, plant tolerance and crop productivity (Bhardwaj et al., 2014; Ajmal et al., 2018; Itelima et al., 2018). In recent years Encapsulated biofertilizers or Nano-fertilizers are also found to be effective (Duhan et al., 2017; Thakur et al., 2018).

Table 1 describes review of the wide array of conventional biotechnology products used for pest management such as (i) Microbial agents, (ii) Bionano-agents, (iii) Natural enemies, predators and entomopathous insects, Parasites, parasitoids and herbivorous/ phytophagus insects, (iv) Sterile Insect Technique (SIT), (v) Botanicals or plant based biocontrol agents, (vi) Biopesticides and (vii) IPM-involving biocontrol agents or biopesticides.

| Control method | Pathogens | Insect-pests and mites | Weeds |
|----------------|-----------|------------------------|-------|
| Microbial agents | antimicrobials (Ahanger et al., 2014; O’Brien, 2017; Aboutarabi, 2018; Shukla et al., 2019) | Entomopathogenic fungi (Dar et al., 2017a; Sultana et al., 2017; Maina et al., 2018) | Microbial herbicides (Patel and Patel 2015; Harding and Raizada, 2015; Trognitz et al., 2016) |
| | Endophytes (Mousa and Raizada, 2015; Braga et al., 2016) | Entomopathogenic nematodes (Gozel and Gozel, 2016); | |
| | Microbial Detoxification of Mycotoxins (McCormick, 2013) | Entomopathogenic Bacteria (Ruiu, 2015); | |
| | | entomopathogens (Lacey et al., 2015); | |
| Bionano-agents | Control of plant pathogens (Alghuthaym et al., 2015; Duhan et al., 2017; Kumar et al., 2017; Oluwaseun and Sarin, 2017) | Insecticidal bacteria (Saiyad, 2017), | |
| | | Microbial agents (Kergunteuil et al., 2016; Gangwar 2017) | |
| | Bionano-insecticidal agents Duhan et al., 2017; Kilherian, 2017; Lade et al. 2017) | | |
| | | Bionano-herbicidal agents (Oliveira et al., 2015; Duhan et al., 2017; Kumar et al., 2017) | |

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Table 1: Conventional biotechnology products used for the management of plant pests (Contd.)

| Control method | Pathogens | Insect-pests and mites | Weeds |
|----------------|-----------|------------------------|-------|
| Natural enemies, predators and entomophagous insects, Parasites, parasitoids and herbivorous/phytophagous insects | natural enemies (Routray et al., 2016; Kenis et al., 2017; van Lenteren et al., 2018), Predators (Ahmed et al., 2016); Parasite-parasitoids (Libersat et al., 2018), entomophagous insect (Hidayat et al., 2018) | Herbivorous insects as natural enemies (Mersie et al., 2017), phytophagous insect (Hidayat et al., 2018) |
| Sterile Insect Technique (SIT) | Control of fruit flies (Sarwar, 2015a; Haymer 2016; Nikolouli et al., 2018) | |
| Botanicals or plant-based biocontrol agents | Plants used in diseases management (Gurjar et al., 2012; Bhagat et al., 2014; Villaverde et al., 2016; Zaker 2016), Phytoalexins (Jeandet et al., 2014; Singh and Chandrawa, 2017) | Insecticidal Plants (Sarwar, 2015b; Villaverde et al., 2016; Hikal et al., 2017), Semiochemicals (El-Shafie and Faleiro, 2017; Murali-Baskaran et al., 2017; Saha and Chandran, 2017), Pheromones (Kirk, 2017), Antifeedants (Koul 2008), Attractants (Drmic et al., 2017), Repellents (Abtew et al., 2015) | Herbicidal plants (Ghosh et al., 2015; Villaverde et al., 2016; Mondale et al., 2018) |
| Biopesticides | Disease control (Villaverde et al., 2016; Damalas and Koutroubas, 2018) | Insect control (Kumar 2015; Tijjani et al., 2016; Nawaz et al., 2016; Villaverde et al., 2016; Damalas and Koutroubas, 2018), Push-pull technology for insect control (Khan et al., 2011, 2014; Pickett et al., 2014; Bhattacharyya 2017) | Weed control (Villaverde et al., 2016) |
| IPM-involving biocontrol agents or biopesticides | Integrated disease management (IDM) (Pandey et al., 2016; Rasool et al., 2018; Dara 2019) | Integrated Insect control (Naifu et al., 2014; Damos et al., 2015; Gangwar, 2017; Dara 2019) | Integrated Weed control (Harker et al., 2013; Lamicchhane et al., 2016; Young et al., 2017; Dara 2019) |

**Molecular Breeding for Pest Management**

Among the pest management strategies mentioned above, host plant resistance (HPR) is one of the best control measures that can also be made more reliable and fast using DNA marker-based breeding methods or molecular breeding. DNA markers can be routinely employed in various aspects of plant genome analysis such as characterization of genetic variability, genome fingerprinting, genome mapping, gene localization, analysis of genome evolution, population genetics, taxonomy, plant breeding, and diagnostics (Jonah et al., 2011; Chauhan and Kumar, 2015). Thus, molecular markers have proven to be invaluable tools for assessing plants’ genetic resources by improving our understanding with regards to the distribution and the extent of genetic variation within and among species.

By using molecular markers, traditional phenotype-based selection methods can be bypassed, which involve growing plants to maturity and closely observing their physical characteristics in order to infer underlying genetic make-up. Lateef (2015) categorized markers into three major groups based on their complexity: (i) Low-Throughput Marker Systems (RFLP), (ii) Medium-Throughput Marker Systems (RAPD, SSR, AFLP), (iii) High-Throughput Marker Systems (SNP, (KASPar, GBS)]. Alternatively, these markers are also classified as non-PCR based approaches (RFLP) and the remaining markers as PCR-based approaches (Chauhan and Kumar, 2015). The advantages and disadvantages of these marker systems are reviewed by some authors (Jonah et al., 2011; Chauhan and Kumar, 2015).

1. Marker Assisted Breeding

Marker-assisted selection (MAS) refer to the use of DNA markers that are tightly linked to target loci as a substitute for or to assist phenotype screening. MAS provides opportunities for enhancing the response from selection because molecular markers can be applied at the seedling stage, with high precision and reductions in cost (Hussain 2015; Lateef, 2015; Lema, 2018). In addition to selection of best traits, markers are also used in the breeding and referred as marker assisted breeding (MAB) or molecular plant breeding (Dwiwedi et al., 2007; Moose and Mumm, 2008; Tiwari 2017). They can also be used as genomics-assisted breeding (Varshney et al., 2005; Peng-fei et al., 2017). Other related molecular breeding methods include mutation breeding in crop improvement (Oladosu et al., 2016; Raina et al., 2016; Lamo et al., 2017); TILLING (Targeting Induced Local Lesions in Genomes) (Rashid et al., 2011; Wanget al., 2012; Sharp and Dong, 2014; Khan et al., 2018a). The use of reverse genetics as applied for breeding is referred as reverse breeding and reverse engineering that lead to accelerated breeding (Dirks et al., 2016).
2009; Gilchrist and Haughn, 2010; Kumari et al., 2018). Selected examples of improved lines/cultivars/varieties developed with resistance to pest and diseases through molecular breeding approaches in some crops are reviewed by Khera et al., (2013).

2. Variants of Plant Resistance to Pests

Using the above-mentioned molecular methods, plants resistance to pests can be obtained faster than the conventional breeding. There are different types of resistance such as multiple, quantitative and durable resistances (Mundt, 2014). Development of durable pest resistant varieties was achieved through gene pyramiding and gene stacking (Pilet-Nayel et al., 2017). Pyramiding entails stacking multiple genes leading to the simultaneous expression of more than one gene in a variety to develop durable resistance expression. Gene pyramiding and gene stacking are sometimes alternatively treated in the scientific literature referring to the same process. Anyways, both involves combining two or more genes of interest into a single plant and the combined traits resulting from this process are called stacked traits (Joshi and Nayak, 2010).

In addition to pest resistance, yield determining genes can also be incorporated in the breeding programs to enhance the yield (Ariizumi et al., 2013; Nadolska-Orczyk et al., 2017) Thus pyramiding of yield affecting genes with other agronomically important genes might be proposed for further improvement. Genetic gain can be improved through enhancing the potential and closing the gaps, which has been evolving and complemented with modern breeding techniques and platforms, mainly driven by molecular and genomic tools, combined with improved agronomic practice (Xu et al, 2017).

Table 2 describes the review of molecular breeding techniques used for developing resistant plant varieties against key pests. These are (i) MAS and MAB, (ii) Multiple resistance, (iii) Quantitative resistance (QR), (iv) Durable resistance, (v) Gene pyramiding and (vii) Gene stacking.

Table 2: Molecular breeding for developing resistant plant varieties against key pests

| Molecular breeding method | Resistance to Pathogens | Resistance to Insect-pests | Resistance to Weeds |
|---------------------------|-------------------------|---------------------------|---------------------|
| Marker Assisted Selection (MAS) and Marker Assisted Breeding (MAB) | MAS in disease resistance breeding (Ragimekula et al., 2013; Farokhzadeh and Fakheri, 2014) | MAS insects resistance in rice (Shabanimofred et al., 2015; Venkanna et al., 2018; Jaiswal et al., 2018) | Striga resistance in sorghum (Yasir and Abdalla, 2013; Yohannes et al., 2015; Ngugi et al., 2016) |
| Multiple resistance | Multiple disease resistance in barley (Steffenson and Smith, 2006), in rice (Singh et al., 2012), in coffee (Alkimim et al., 2017); implications in MAS (Ali et al., 2013) | multiple insects resistance in maize (Badji et al., 2018) | multiple resistances to herbicides (Gressel, 2000; Neve et al., 2009) |
| Quantitative resistance (QR) | Dissection and adoption in maize (Yang et al., 2017), molecular bases of QR (Vasquez et al., 2018) | Resistance to leaf hoppers, and brown plant hopper (Fujita et al., 2009; Dhillon and Sharma, 2012) | Resistance to orobanche (Louran et al., 2016; Fernández-Aparicio et al., 2016) |
| Durable resistance | Durable management of pathogens (Kou and Wang 2010; Mundt, 2014; Consortium 2016) | Durable management of insect-pests (Mundt, 2014; Sandhu and Kang, 2017) | Durable Sunflower resistance to orobanche (Velasco et al., 2016) |
| Gene pyramiding | Durable Resistance to pathogens (Mekonnen et al., 2017; Pilet-Nayel et al., 2017) | Pyramiding of two insect resistance genes in rice (Xu 2013; Liu et al., 2016) | Pyramiding of Striga resistance genes (Yasir and Abdalla, 2013; Yohannes et al., 2015; Ali et al., 2016) |
| Gene stacking | Enhancing resistant to diseases (Consortium 2016; (Das et al., 2017) | Insect resistance in rice (Das and Rao, 2015) | stacked herbicide resistant traits (Chauhan et al., 2017) |
**Genetic Engineering for Pest Management**

Genetic engineering, also called genetic modification, is the techniques of direct, controlled and artificial modification and manipulation of an organism's genes which is used to change the genetic makeup of cells, including the transfer of genes within and across species boundaries to produce improved or novel organisms. Thus, plant genetic engineering is a technology where the genome of a host crop is engineered with a foreign donor gene regulated by certain gene regulatory sequences. There are different variants of genetic engineering based on the difference of the gene donor and recipients namely transgenics, intragenics, cisgenics and subgenics.

1. **Transgenics**
   Genetic engineering techniques involving gene transfer of foreign gene from unrelated species are referred as transgenics. Most of the GM products of the past two decades belong to this category of genetic engineering. Dramatic progress has been made over the past two decades in manipulating genes from diverse and exotic sources, and inserting them into microorganisms and crop plants to confer resistance to pests, tolerance to herbicides, drought, soil salinity and aluminum toxicity; improved post-harvest quality; enhanced nutrient uptake and nutritional quality; increased photosynthetic rate, sugar, and starch production; increase defectiveness of biocontrol agents; improved understanding of gene action and metabolic pathways; and production of drugs and vaccines in crop plants (Sharma et al., 2012). These are further elaborated after few sections.

2. **Intragenics, Cisgenics and Subgenics**
   There are several other GE techniques that involve gene transfer between closely related species or within same species. Recently, cisgenesis and intragenesis have been developed as new tools aimed to modify crops in response to the major concerns of the general public about transgenic crops relates to the mixing of genetic materials between species that cannot hybridize by natural means. While cisgenesis involves genetic modification using a complete copy of natural genes with their regulatory elements that belong exclusively to sexually compatible plants (same crop species), intragenesis refers to the transference of new combinations of genes and regulatory sequences belonging to that particular species (belonging to the same breedable gene pool). Both concepts imply that plants must only be transformed with genetic material derived from the species itself (cisgenic) or from closely related species capable of sexual hybridization (intragenic) (Holme et al., 2013).

Regardless of which of the genome editing systems (described below) are used, the crop that is genome edited is called “subgenic” (Sticklen, 2015). As mentioned below, the technology associated with development of subgenic crops is a fast-growing technology with a hope to result in the crops of the 21st century that can meet the needs to feed the ever growing world population with the least controversies and public concerns. So far, application of cisgenesis and intragenesis as alternatives to conventional transgenesis are limited to a few species, mainly due to the lack of knowledge of the regulatory sequences required (Espinoza et al., 2013; Holme et al., 2013; Sticklen, 2015).

There are substantial differences in the biosafety and regulatory issues on transgenics, cisgenics, intragenics and subgenics. Countries considerable vary in implementing either prohibitive and stringent or encouraging and promoting biosafety regulations.

3. **RNA Interference (RNAi)**
   Several functional genomics tools were developed in the recent past that offers specificity and efficacy in silencing members of a gene or multiple gene family. Gene suppression via RNA interference (RNAi) is a method of blocking gene function by inserting short sequences of RNA that match part of the target gene’s sequence, thus no proteins are produced. RNAi has provided a way to control pests, introduce novel plant traits and increase crop yield (Younis et al., 2014; Meena et al., 2017).

4. **New Breeding Techniques and Genome Editing Technologies**
   A range of new genetic modification techniques (nGMs) or new breeding techniques (NBTs) have been rapidly developed in recent years and used to modify the genetic make-up of a plant variety in a more precise way in order to introduce new traits or modify existing ones. These techniques have efficiently accelerated improvement of crop varieties with various useful traits (Georgesand Ray, 2017; Townson, 2017). The development of these nGMs or NBTs has raised worldwide discussions regarding their regulation in which different existing regulatory frameworks for GMO cover nGMs to varying degrees (Eckersforster et al., 2019).

NBTs include emerging techniques that are more broadly and commonly referred to as ‘genome editing’ that aim to manipulate DNA at specific locations to rapidly generate potentially useful traits. Genome editing of crop plants is a rapidly advancing technology whereby targeted mutations can be introduced into a plant genome in a highly specific manner and with great precision (Georges and Ray, 2017; Townson, 2017; Jansing et al., 2019). Genome editing, which consists of targeting and digesting DNA at a specific site in the genome is an important tool for improved basic understanding of plant gene function analysis. Thus, it is a more precise and accurate technology to effectively develop more productive, highly nutritious and climate-resilient crops (Wolter et al., 2019). However, the regulatory framework that covers genome-edited crops in different countries has a major impact on their development and marketability (Jansing et al., 2019).
Eckerstorfer et al., (2019) listed the range of nGMs techniques namely (i) Genome editing with site-directed nucleases (SDNs), e.g., using clustered regularly interspaced short palindromic repeat (CRISPR)- associated protein-9 (CAS) system directed nucleases, transcription activator-like effector nuclease (TALENs), zinc-finger nucleases (3 ZFNs) or meganucleases. SDN-based techniques can also be applied for multiplex genome editing and “base editing” as well as for modification of transcriptional regulation; (ii) Genome editing directed by synthetic oligonucleotides, referred to as oligonucleotide-directed mutagenesis (ODM) also known as the Rapid Trait Development System (RTDS); (iii) RNA dependent/directed DNA methylation (RdDM); an approach for modifying epigenetic regulation of gene expression; (iv) Cisgenesis and intragenesis; (v) Transgrafting, in particular the use of GM-rootstocks in grafting; (vi) Agro-infiltration, (vii) Haploid induction and accelerated breeding, i.e., examples of techniques developed to assist complex breeding schemes

Among these genome-editing technologies, the CRISPR–Cas9 system has become the tool of choice for gene manipulation and has been extensively used in the last five years because of its, novelty, simplicity, affordability, and feasibility (Sticklen, 2015; Barakate and Stephens, 2016; Bernard et al., 2019). The highly precise nature of the genome editing technology CRISPR-Cas enables an unparalleled level of control over the mutation process, allowing immediate pyramiding of multiple beneficial traits into an elite background within one generation (Wolter et al., 2019). CRISPR technology is constantly advancing including options for various genetic manipulations like generating knockouts; making precise modifications, multiplex genome engineering, and activation and repression of target genes. It has been used for plant nutritional improvement, enhancement of plant disease resistance and production of drought tolerant plants (Arora and Narula, 2017; Byers 2019; Hahne et al., 2019).

Table 3 describe the review of the application of some of the new genetic medication techniques (nGM) or new breeding techniques (NBTs) (i) RNAi, (ii) Cisgenics and intragenics, (iii) Gene editing in general, (iv) Genome editing specifically using CRIPR Cas9 in pest management.

| Genetic engineering method | Resistance to Pathogens | Resistance to Insect-pests | Resistance to Weeds |
|----------------------------|-------------------------|---------------------------|---------------------|
| I. Genetic engineering techniques of the past two decades | Disease resistance (Vincelli, 2016; Scott et al., 2016; Sniezko and Koch, 2017; Dong and Ronald, 2019) | insect pest management (Mabubu et al., 2016; Dar et al., 2017b; Sniezko and Koch, 2017; Alphey and Bonsall, 2018) | Herbicide-resistant crops (Kniss 2018; Fartyal et al., 2018) |
| Transgenics | Diversity in effector genes of banana disease (Stergiopoulos et al., 2014), and potato disease (Yang et al., 2018) | Understanding of the evolution of insect epigenetic systems (Hunt et al., 2014) | Glyphosate resistance in Chile-pepper (Ortega et al., 2018), sugarcane resistance to herbicide (Dermawan et al., 2016) |
| Intragenics | Genes discovery for cisgenic crops (Kushalappa et al., 2016); Cisgenic potato resistance to late blight (Jo et al., 2014; Gheysen and Custers, 2017) | Insect resistance (Ni et al., 2011) | |
| Cisgenics | Cisgenic apple resistant to fire blight and scab (Vanblaere et al., 2014; Kost et al., 2015) | Insect Pest Management (Das 2015; Thakur et al., 2016; Jaba and Sharma, 2017) | Parasitic weed management (Aslam et al., 2016; Westwood et al., 2018) |
| RNAi | Plant disease resistance (Duan et al., 2012; Seo et al., 2013) | Insect Pest Management (Das 2015; Thakur et al., 2016; Jaba and Sharma, 2017) | |
| II. New Breeding Techniques (NBT) developed recently | Understanding Plant-Pathogen Interactions (Barakate and Stephens, 2016; Ghimire 2017; Borrelli et al., 2018; Langner et al., 2018) | Insect control (Chen et al., 2016; Sun et al., 2017) | Weed management (Butt et al., 2018; Neve, 2018) |
Biotechnology for Food Security and Sustainable Development

The Scope of Biotechnology, GMO and Genetic Engineering

Biotechnology can be used to create many technologies, and GMOs are just one example. Crops that undergo artificially DNA modifications or genetic engineering for beneficial traits improvements are considered as genetically modified (GM) crops. To create a GMO, researchers use genetic engineering technique to turn off an existing gene or add a gene from another source to create a new, desirable characteristic in a product. Genetic engineering has the potential to address the critical constrains of sustainable agriculture and the need for sufficient quantity of healthy food, feed, and biomass feedstock for the industry as well (De Buck et al., 2016).

The previous sections are clearly witnessing that biotechnology is more than genetic modification or genetic engineering. Indeed, some of non-genetic transfer aspects of plant biotechnology are potentially the most powerful and the most beneficial such as molecular characterization of pests and tissue culture techniques. There are numerous applications that do not involve genetic modifications. However, it is to be noted that among these applications the use of recombinant DNA technology or transgenic or genetic engineering is the most post powerful and influential for the efficiency and effectiveness of agricultural production and productivity. Biotechnology has therefore opened an exciting frontier in agriculture for maintaining healthy plants that can result in enhanced crop yields and enriched nutritional compositions with an ultimate aim of feeding the ever-growing population.

In general GM plants are divided into three groups, depending on the purpose of its generation. GM plants of first generation are those with input traits basically related to increase insect and herbicide resistance, which is the subject of this review article. GM plants of second-generation present output traits related directly to benefit the consumer, aiming mainly to add value to the final product through nutritional improvement or better storage conservation. GM plants of third generation can be so called “green factories” and be used in the production of novel products, like pharmaceuticals and biofuels in an environmentally sustainable manner (Caserta and de Souza, 2017). The last two are sometimes categorized as products of molecular farming and synthetic biology. The ultimate goals of synthetic biology is to design and build engineered biological systems that process information, manipulate chemicals, fabricate materials and structures, produce energy, provide food, and maintain and enhance human health. It can be used in agriculture to modify plants via transgenic seeds to produce specialty chemicals and biofuels, and novel pest control strategies (Goold et al., 2018; Wang and Zhang, 2019). Similarly plant molecular farming describes plants as bioreactors for the production of recombinant proteins and other secondary metabolites for commercial and pharmaceutical purposes (Alireza and Nader, 2015; Buyel, 2019).

In general the focal areas and scope of the application of plant biotechnology include (i) Nutritional enhancement and functional foods, (ii) Abiotic stress tolerance, (iii) Increased digestibility, (iv) Increased volumes of biomass for biofuel, (v) Better fiber quality, (vi) Flower color and scent modification, (vii) Production of industrial and pharmaceutical compounds, (viii) Less allergenicity, (ix) Enhanced food flavor and aroma, (x) Healthier oils and (xi) Phytoremediation or bioremediation (Navarro and Hautea, 2011).

More comprehensively, genetic engineering techniques have been used for improved resistance to biotic stresses (Tohidfar and Khosravi, 2015; Alemayehu 2017; Bhattacharjee et al., 2017), biotic and abiotic stress (Dutta and Roy, 2016; Parmar et al., 2017; Wijeratnha-Yapa, 2017). A similar review on the applications of biotechnology related to management of abiotic stresses, agronomic traits and quality improvements and other beneficial characteristics are under preparation, which will be reported separately elsewhere. Whereas the benefits of GM crops related to pest management are described in Table 4 below.

As mentioned above plant products of biotechnology have been available in the market for 23 years since 1996. There are 29 different crops and fruit trees in 42 countries, which have been successfully modified for various traits like herbicide tolerance, insect-pest resistance, disease resistance and quality improvement (Nazir et al., 2019). Some of these GM traits related to pest management are indicated in Table 4. GM traits related to quality improvements and other characteristics are not included here which will be reported elsewhere.

Concerns and Controversies on The Safety/Risks of GMO

Ever since GMO products first released in 1992 and widely commercialized in 1996, there have been some biased concerns on their risks lead by campaigns of anti-groups fueled by fear of the fierce competition. Apparently, review of several studies conducted in EU countries concluded that “GM products are not inherently less safe (or not riskier) than those developed by traditional breeding”. The main conclusion to be drawn from the efforts of more than 130 research projects, covering a period of more than 25 years of research, and involving more than 500 independent research groups, is that biotechnology, and in particular GMOs, are not per se more risky than conventional plant breeding technologies (EU, 2010). Similarly, a study based on 15 years of intense research and risk assessment revealed...
that GM crops do not pose greater risks for human health or the environment than traditionally bred varieties (Adenle, 2015).

Regardless of the huge resources invested to curb the progress of GMO production and reverse the innovations, the weight of the evidence in favor of their safety is overwhelming, as reflected in the position statements of diverse, prestigious scientific societies, scientific review papers, and hundreds of peer-reviewed research papers (Hallerman and Grabau, 2016; Vincelli, 2016; Caserta and de Souza 2017). Accordingly, Vincelli (2018) compiled the positions of several National Academies, professional associations, Scientific Boards ... etc that declared “there is no scientific evidence and reproducible studies whatsoever that current GE foods, or ingredients made from GE crops pose any risk to humans, animals and environment. They are not different in nature from those created by conventional breeding practices”. Indeed, rigorous scientific risk assessment and risk-management regulations/guidelines are in place that nullify the “fear of unknowns”. The safety of GM crops is confirmed by peer-reviewed studies usually conducted for 2-4 years and consume most of the product development cost.

Terefe (2018) indicated the list of concerns related to risks to environment, human health, food/feed safety, social, economic and political concerns and recommended case-by-case analyses. It is to be noted that the safety assessment of GM foods generally focuses on: (i) direct health effects (toxicity), (ii) potential to provoke allergic reaction (allergenicity); (iii) specific components thought to have nutritional or toxic properties; (iv) the stability of the inserted gene; (v) nutritional effects associated with genetic modification; and (vi) any unintended effects which could result from the gene insertion. In general, the approaches involve (i) Bioinformatics, (ii) Digestibility/degradation, (iii) Metabolomics, (iv) Feeding trials, (v) Field trials. There are no mysterious and undetectable risks that can escape from these scientific evaluations. Reliable biotechnological method have also be developed for identification of GM crops for biosafety and legitimacy of transgenes (Fraiture et al., 2015; Lin and Pan 2016; Nazir et al., 2019).

| Crop                  | Common Use                          | Application of GM traits targeting pest management |
|-----------------------|-------------------------------------|--------------------------------------------------|
| Alfalfa               | Animal feed                         | Disease management: Fungus resistance            |
| Apple                 | Food                                | Insect resistance                                |
| Canola                | Cooking oil, Margarine, Emulsifiers in packaged foods | Herbicide tolerance                             |
| Cotton                | Fiber, Cotton seed oil, Animal feed | Cotton bollworm resistance                       |
| Maize                 | high-fructose corn syrup, corn starch, Animal feed | corn borer resistance                            |
| Papaya                | Food                                | Papaya Ring Spot Virus                           |
| Potato                | Food                                | Late blight fungus and Virus resistance          |
| Soybean               | Soybean oil, Animal feed            | Soybean dwarf virus and Phytophthora fungus resistance |
| Squash                | Food                                | Cucumber Mosaic Virus resistance                 |
| Sugar beet            | Food                                | Herbicide tolerance                             |

Genetically modified crops that have not yet been widely cultivated

| Crop                  | Common Use                          | Application of GM traits targeting pest management |
|-----------------------|-------------------------------------|--------------------------------------------------|
| Bean                  | Food                                | Insect resistance                                |
| Cowpea                | Food                                | Insect resistance (pod borer (Maruca vitrata))    |
| Egg plant             | Food                                | Insect resistance                                |
| Linseed               | Food                                | Herbicide tolerance                             |
| Plum                  | Food                                | Virus (plum pox virus) resistance                |
| Rice                  | Food                                | Bacterial blight and Fungal disease resistance   |
| Tomato                | Food                                | Bacterial spot resistance, viral disease resistance |
| Wheat                 | Food                                | Powdery mildew resistance                        |

Source: Tohidfar and Khostravi (2015), Mekonnen et al., (2017); ISAAA (2018); Nazir et al., (2019)
On the contrary, concerns over the lack of knowledge on the safety of GM crops are used as arguments to ban them, or at least to regulate them heavily. Many citizens, politicians and countries generally take those arguments to reinforce misconceptions about GM crop. In this regard Sanchez and Parrott (2017) and Valentinov et al., (2018) analyzed the critiques on anti-GMO advocacy and scientific studies usually cited as evidence of adverse effects. Accordingly, a total of 35 studies represent fewer than 5% of all published studies assessing GM food/feed safety were analyzed by Sanchez and Parrott (2017). It was found that most studies often used in the public debate against GM food/crops have been published in journals with lower visibility; eight were even published in journals without a listed impact factor. In general terms, all papers analyzed violate at least one of the basic standards for assessment of GM food/feed safety mentioned above. On the other hand, Valentinov et al., (2018) revealed that the anti-GMO advocacy usually involves NGOs having diverse competitive agendas.

**Continuous Increasing Trend of GM Crops Production Over the Past 23 Years**

Interestingly, the benefits and production areas of GM are substantially increasing. Accordingly, a total of 70 countries adopted biotech crops through cultivation and importation in 2018, the 23rd year of continuous biotech crop adoption, according to the Global Status of Commercialized Biotech/GM Crops in 2018 (ISAAA Brief 54) released by the International Service for the Acquisition of Agri-biotech Applications (ISAAA). Twenty-six countries (21 developing and 5 industrialized countries) planted 191.7 million hectares of biotech crops, which added 1.9 million hectares (4.7 million acres) or 1% from 189.8 million hectares) to the record of plantings in 2017. The first 23 years of commercialization of biotech crops (1996 to 2018) has confirmed that biotech crops have delivered substantial agronomic, environmental, economic, health, and social benefits to farmers, and increasingly to the consumers. The continuous adoption of biotech crops by farmers worldwide indicate that biotech crops continue to help meet global challenges of hunger, malnutrition, and climate change (ISAAA, 2018). Global area of biotech crops has increased ~113-fold from 1.7 million hectares in 1996 to 191.7 million hectares in 2018 – this makes biotech crops the fastest adopted crop technology in recent times. An accumulated 2.5 billion hectares or 6.3 billion acres were achieved in 23 years (1996-2018) of biotech crop commercialization. This increase is due primarily to greater profitability stemming from higher commodity prices, increased global and domestic market demand, and available seed technologies (Raman, 2017; Smyth, 2017; ISAAA, 2018).

Figs. 1-3 show the global map of Biotech crop countries and mega-countries, indicating the type of crops and area of production (hectare), top 5 countries and info-graphics as described by ISAAA (2018).
Genetic engineering (GE) offers an expanding array of strategies for enhancing pest resistance of crop plants in sustainable ways, including the potential for reduced pesticide usage. Thus, pest management has changed dramatically during the past 23 years by the introduction of transgenes into crops for the purpose of pest management. GE crops are efficiently used in complementary to a diversified IPM plan (Kos et al., 2009). Despite the advantages of improving the efficiency of pest control, there are also challenges for successful implementation and sustainable use. One of the biggest challenges for sustainable use of the technology is the evolution of resistance. In this regard, challenges and solutions for successful implementation of an IPM approach were recently reviewed, in which the solutions include refuge compliance (Jin et al., 2015; Li et al., 2017; Reisig, 2017) and proper stewardship program (Anderson et al., 2019). According to ETS (2013) Stewardship program involve considerations at each of the seven stage of the Product Life Cycle namely (i) Research and Discovery, (ii) Product Development (iii) Seed or Plant Production (iv) Marketing and Distribution, (v) Crop Production (vi) Crop Utilization (vii) Product Discontinuation.

**Contribution of Biotech Crops to Sustainable Development**

Meta-analysis of 147 studies during the past 20 years on Soybean, Maize, Cotton: multitude of benefits revealed that the use of GMO reduced pesticides use by 37%, increased yields by 22%, increased farmer profits by 68% (Klümper and Qaim, 2014). Various review reports showed the role of biotechnology in food security (Abah et al., 2010; Tonukari and Omotor, 2010; Najaf and Lee, 2014; Cano et al., 2017; Gartland and Gartland, 2018) and in sustainable development (Sharad et al., 2010; Adenle, 2015; Björnberg et al., 2015). Similarly, the contribution of GMO in food security has been reviewed by several scholars (Qaim and Kouser, 2013; Lamichhane, 2014; Hallerman and Grabau, 2016; Ouyang et al., 2017; Raman, 2017; Repalli, 2017; Smyth 2017; Gartland and Gartland, 2018; Terefe, 2018). Similarly, the present review is aiming...

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**Fig. 2:** Top 5 Countries that planted Biotech crops in 2018 (area and adoption rates). [Source: ISAAA, 2018]

**Fig. 3:** Infographics of the global status of commercialized GM crops 2018.
at presenting the comprehensive and exhaustive account of these diverse applications that witnessed tremendous contribution of biotechnology and GMO in food security and sustainable development. Biotech crops, developed with improved traits such as increased yield, more resistance to pests, improved nutrition, among others, are undeniably necessary to address these global challenges affecting the lives of so many families globally (ISAAA, 2018; Gebretsadik and Kiflu, 2018). The contributions of GM crops in some countries were reviewed recently (Shetty et al., 2018; Anderson et al., 2019). It can be witnessed that the commercial applications of GM to horticultural crops lag far behind those of agronomic crops. In some respects, this is to be expected, since the majority of research and investment has been directed to commodities with the commercial value (Gaur et al., 2018; Shetty et al., 2018).

Biotechnology can also help conduct organic food production. Thus, organic farming can be achieved with the use of biotechnological tools (Dubey, 2014; Cano et al., 2017; Taheri et al., 2017). In this regard pest management (Brzozowski and Mazourek, 2018), durable molecular breeding (Gheysen and Custers, 2017) are also useful for organic farming. On the other hand, nanobiotechnology has been applied for crop production and precision agriculture (Duhan et al., 2017; Elemike et al., 2019; Sanzari et al., 2019; Shang et al., 2019) and plant disease management (Worralle et al., 2018). During the past two decades various application of biotechnology have provided reliable solutions to the management of several biotic and abiotic factors. It is to be noted that biotechnology or genetically engineering or GMO is not a panacea (cure-all) or silver bullet or magic bullet for addressing all agricultural constraints. Rather, it should be seen as one of the many undeniable modern tools available for use as the priority enabling strategy that immensely contributes to sustainable development.

Sustainable development is consisting of three interlinked dimensions namely economic profitability, social equity and environmental health aspects. Sustainability rests on the principle that we must meet the needs of the present without compromising the ability of future generations to meet their own needs (Björnberg et al., 2015). To this end, biotechnology is providing the building blocks for sustainable development as it can balance developmental needs (social and economic dimensions viz-a-viz food, feed and fiber production, renewable raw materials and energy) and environmental conservation (environment friendly technologies such as pollution prevention, and bioremediation).

In conclusion, as we are leading a competitive Knowledge based economy, doing things as usual cannot take us anywhere. Scientific advances are continuously witnessing that Knowledge and skills are always dynamic and new breakthroughs/innovations are emerging every day for humans to sustainably tap their natural resources and combat food insecurity and hunger. Some of the most disastrous nature’s challenges can be addressed upon rigorous advanced scientific studies fueled by new breakthroughs. To this end, instead of being confused with unscientific advocacy of side effects, it is always helpful and mandatory to develop the necessary capacity (skilled manpower, infrastructure, policy and regulations) in order to harness the technology and better cope up with the inevitable emerging and outbreaks of pests that severely threaten sustainable development. It is only through continuous harnessing of such novel technologies that sustainable development can be achieved.

**Conflict of Interest**

The authors declare that there is no conflict of interest with present publication.

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