

CRISPR-BASED SOLUTIONS FOR AGRICULTURE: A SYSTEMATIC REVIEW

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Abstract— CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) emerges as a tool for agriculture. Applied to plant breeding, this technology has the potential to increase productivity cost-effectively within a short timeframe. The objective of this study was to assess the biotechnological potential of CRISPR-based solutions in agriculture through a systematic review. The search was performed on February 2021 using the keyword "plant breeding AND CRISPR" in the title, abstract, and/or keywords of scientific publications - and analyzed using the statistical package Bibliometrix in R software - and the front page of patent files. A total of 348 scientific articles were retrieved from the Scopus and Web of Science databases. And 63 patented innovations were retrieved from the WIPO (World Intellectual Property Organization) database. The number of articles and patents has increased exponentially throughout the years. China has the lead in R&D (research and development) in the field, followed by the United States, Japan, Germany, France, and Canada. CRISPR has been mostly employed in studies of genome editing of crops such as maize, potato, tomato, rice and, soybean and innovations for rice, tomato, alfalfa, and mung bean. Patent registers were mostly related to code C12N and A01H of the International Patent Code. Genome editing via CRISPR has been established as a highly relevant tool for biotechnology. The research and development of CRISPR-based solutions in agriculture are on an ascending curve. This study represents the current scenario and may be expanded in the future to support policymakers and R&D investments.

Keywords—Biotechnology, CRISPR/Cas, Patent, Plant Breeding.

1 INTRODUCTION

Plants are a wide font of resources for human life, providing food, medicine, and fuel. However, future climate scenarios predict a significant impact on the productivity of cultivated plants. Climate change predictions indicate the intensification of drought, decrease of arable land, and shortage of available water for agriculture (DAI, 2013). In addition, population growth and the conversion of the economy to sustainable practices using renewable resources will demand higher productivity of plant cultivars (LENAERTS; COLLARD; DEMONT, 2019).

Throughout centuries plants have been cultivated and bred to improve productivity. However, the intense selection of characteristics of agricultural interest has limited crop diversity and breeding possibilities (LOUWAARS, 2018). More recently, the use of molecular approaches of mutation and transgenic breeding have been employed in modern agriculture. Genome editing techniques such as Zinc Finger Nucleases (ZFN) and Transcription Activator-Like Effector Nucleases (TALEN) have made it possible to target genes of

characteristics of interest more precisely (SANAGALA; MOOLA; BOLLIPO DIANA, 2017).

Despite the advances brought by these technologies, the genetical improvement in plant productivity is not as fast and the increase in demand, as per the 2008 food crisis (DIBDEN; GIBBS; COCKLIN, 2013). Either due to laborious and expensive breeding techniques or long and costly regulatory processes for genetically modified organisms (GMO), there is yet a need to improve genome editing for efficiency in plant production.

CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) emerges as a powerful tool for genome engineering (CHEN, K. *et al.*, 2019). Derived from bacterial and archaea immune systems, this tool is an RNA-guided platform for highly efficient and specific genome editing and regulation in diverse organisms. The technique enables the manipulation of nearly any sequence in the genome to reveal its function and target genes in regulatory networks, signal transduction, and metabolite production (WANG; LA RUSSA; QI, 2016). Since 2013, CRISPR has been successfully employed in model and crop plant species – *Arabidopsis*, tobacco, rice, maize, wheat, grape, potato, tomato, soybean, and others (BORRELLI *et al.*, 2018; LI *et al.*, 2019; REN *et al.*, 2019; ZHOU *et al.*, 2020) – screening mutants with altered phenotypes, enabling function analysis and generation of new crop varieties. And last year, researchers Jennifer Doudna and Emmanuelle Charpentier were awarded the Nobel Prize in Chemistry for their discovery of CRISPR as a tool for biotechnology.

The insertion of point mutations and gene replacements using CRISPR are of great value for functional genomics studies in plants and may help to identify agronomically valuable traits. Plant breeding based on function genomics is faster and more precise for the creation of improved genetic varieties because it allows for marker-assisted selection. Consequently, the use of CRISPR for function genomics can be employed in the identification of the molecular basis of plant adaptation and productivity, more easily and precisely than other methods. And the information could be used by breeders for a more focused traditional molecular breeding, avoiding public concerns, as well as regulatory hurdles of transgenic organisms (JAGANATHAN *et al.*, 2018).

Also, in an attempt to facilitate the commercialization of GMOs, transgene-free genome editing using CRISPR has been applied. The method delivers purified CRISPR/Cas9 ribonucleoproteins (RNPs) into plant protoplasts via PEG-mediated transformation. And, thus, edits genes without involving foreign DNA, as it has been applied in apple and grape (MALNOY *et al.*, 2016; OSAKABE *et al.*, 2018). However, due to reports of low efficiency in mutagenesis, this technique requires further development.

Therefore, considering the potential for plant productivity improvement through CRISPR genome editing, the objective of this study was to assess the biotechnological potential of CRISPR-based solutions in agriculture through a systematic review of scientific articles and patented technology.

2 THEORIES

Advances in research leading to innovation in methods and products have been exponentially increasing with CRISPR tools. The combination of traditional technology and research strategies with this tool indicates a path to innovation driven by global productivity growth and food security (GUPTA *et al.*, 2020).

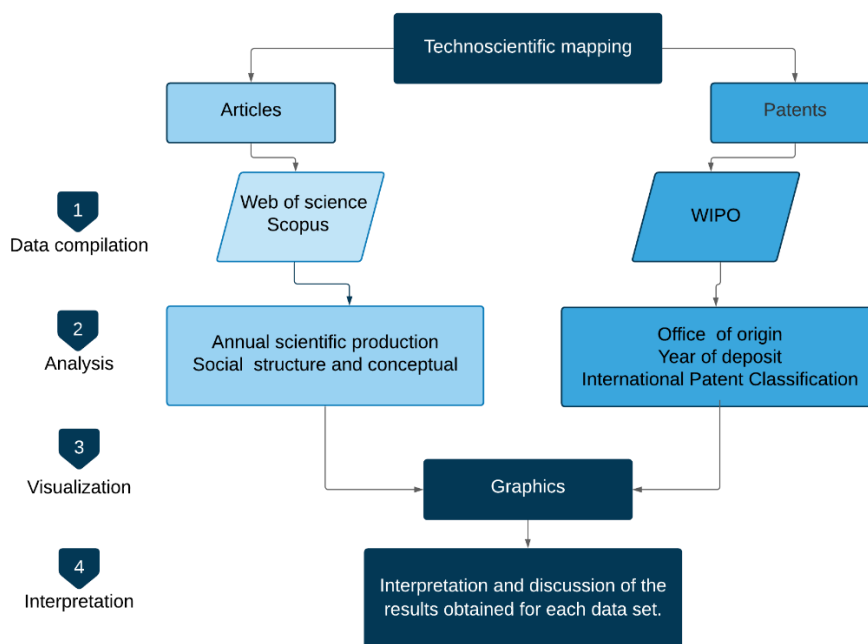
The licensing of new products, however, may not be related strictly to demand but investments and regulatory endorsements. Despite its cost-effectiveness and early-stage success as biotechnology, CRISPR-based innovations are further developed in regions with established policies and funds for research and development (R&D).

A systematic review is a research conducted to identify and retrieve information regarding a relevant subject. Its systematic nature uses statistical methods to minimize bias to provide more reliable conclusions applied to decision-making processes (HIGGINS, 2019). In the field of agriculture, the assessment of technological improvements through mapping and analyses of scientific and patent publications is highly relevant. The analysis of innovation through patent deposits helps investment decisions in the sector. And employing tools of a systematic review is possible to obtain a view of the current scenario, identify knowledge gaps, and forecast technological trends.

3 METHODOLOGY

This study was based on the research of scientific articles and patents deposited in public data repositories. It is composed of four stages: (1) Data compilation; (2) Analysis; (3) Visualization and, (4) Interpretation (Figure 1).

Figure 1. Stages of the methodology applied to the technoscientific mapping via systematic review.



Source: Souza (2021).

The search was performed on February 2021 using the keyword "plant breeding AND CRISPR" in the title, abstract, and/or keywords of scientific publications and front page of patents. There was no timeframe established aiming at the highest number of information.

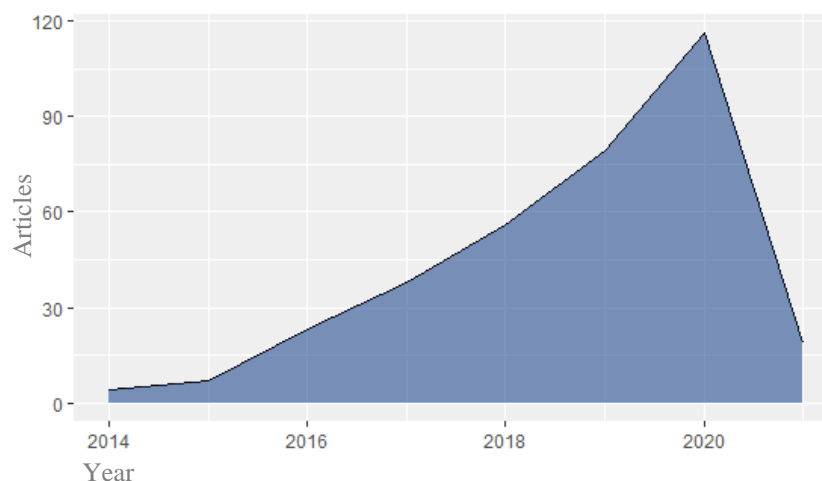
The scientific articles were prospected at the Scopus (<http://www.scopus.com>) and Web of Science (<http://www.webofknowledge.com>) databases. The data obtained for the search term was exported as a BibTex file, combined in one data set, and analyzed using the statistical package Bibliometrix in R software (ARIA; CUCCURULLO, 2017). The papers were revised to remove duplicates and files not corresponding to the objective of this study. Annual scientific production, social and conceptual structure were analyzed.

Patents were prospected and analyzed at the World Intellectual Property Organization (WIPO) database, covering publications in 87 offices and the European Patent Office (EPO), Organisation Africaine de la Propriété Intellectuelle (OAPI), African Regional Intellectual Property Organization (ARIPO), Eurasian Patent Organization (EAPO) and Chandigarh Group of Colleges (CGC) databases. Multiple data crossing and visualization graphs were obtained. There was also no timeframe established aiming at the highest number of information. Patent files were revised to remove duplicates and files not corresponding to the objective of this study. The final set was computed regarding the country of origin, year of deposit, and International Patent Classification (IPC) code.

4 DISCUSSION AND RESULTS

Scopus and Web of Science retrieved 137 and 281 scientific publications, respectively. After removing duplicate files, a total of 348 publications were used for the analysis (Figure 2). The files corresponded to articles published between 2014 and 2021, indicating a high relevance of this technology since its implementation.

Figure 2. Annual scientific production of articles published for “plant breeding AND CRISPR” and indexed in the Scopus and Web of Science databases.



Source: Souza (2021)

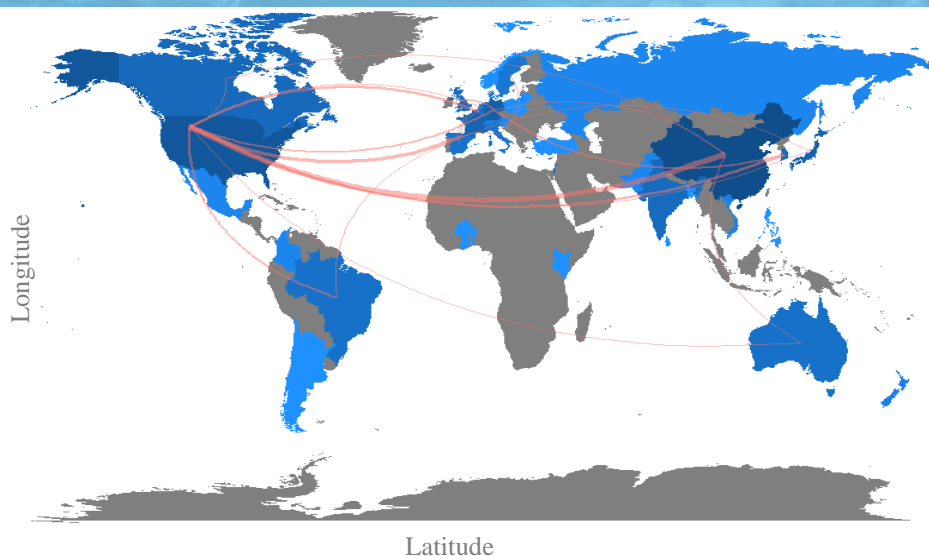
Publications have an annual percentage growth rate of 24.93. The largest number of publications was registered in and in 2020 (116). They were developed by 1,493 authors with a collaboration index of 4.58.

To study the social structure and collaboration networks in publications about CRISPR, authors and their affiliations were examined, at least two collaborations were considered to form the network. The articles have as corresponding authors, researchers from countries such as China (121), United States (40), Japan (26), Germany (25), France (16), Canada (15), India (11), Korea (10), Israel (9) and United Kingdom (8) (Figure 3).

Among the countries of South America, Brazil is the only one that is part of the network of collaborations. A high percentage of major crop plantations (soy, corn and cotton) are composed of transgenic plants in Brazil. Nonetheless, there is still a long regulatory process for genetically modified organisms – and CRISPR-based innovations are analyzed by a dedicated group of specialists within the national committee. There, each cultivar developed by a new breeding technique, such as CRISPR, is analyzed and considered a GMO in a case-by-case situation (MOLINARI *et al.*, 2020).

In the European Union, for instance, regulations for GMOs are applied to CRISPR-edited crops, which might have an impact on research investments (PURNHAGEN; WESSELER, 2020). However, with discussions to change this regulation ongoing, countries like Germany are anticipating their participation in the field. The application of genome editing and CRISPR technologies for the productivity of crops, stabilization of yield and improvement of resistance to pathogens, tolerance to abiotic stress, and, also, the preservation of locally adapted varieties were incentivized through the *Regulations governing the funding of plant research projects in “Crops for the Future”* under the National Research Strategy BioEconomy 2030 by the German government.

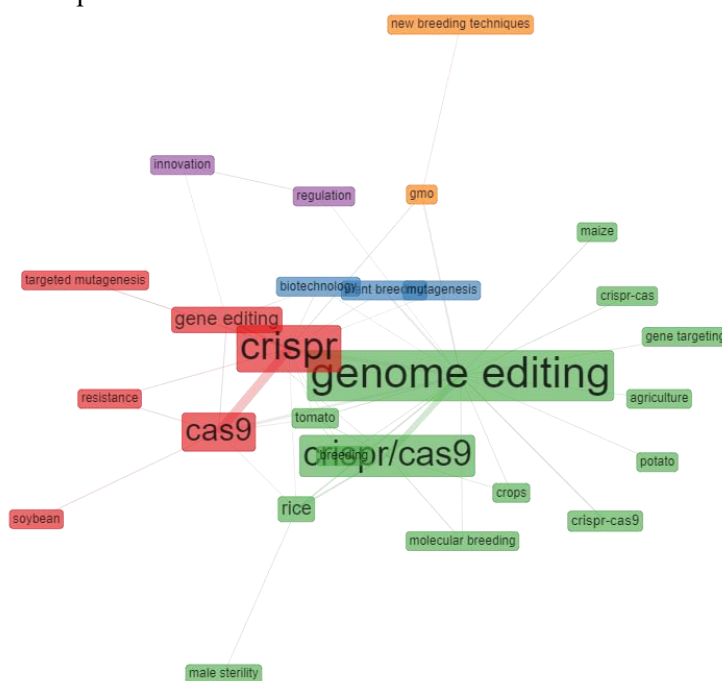
Figure 3. Geographic origin and collaboration network of articles published for “plant breeding AND CRISPR” and indexed in the Scopus and Web of Science databases.



Source: Souza (2021)

The network of co-occurrence analysis of the author's keywords was used to understand the conceptual structure of publications on CRISPR. For this analysis, 991 keywords from the analyzed document collection were considered, 50 of these were mentioned at least three times and formed the network (Figure 4). The font size indicates the frequency of use of the keywords, the lines represent the relationship networks of the words with each other, and the position indicates how much they are in the center or on the periphery of the network.

Figure 4. Co-occurrence analysis of keywords in articles published for “plant breeding AND CRISPR” and indexed in the Scopus and Web of Science databases.



Source: Souza (2021)

The co-occurrence analysis of words finds connections between concepts that occur simultaneously in document titles, keywords, or abstracts. Therefore, uses the actual content of the documents to build a

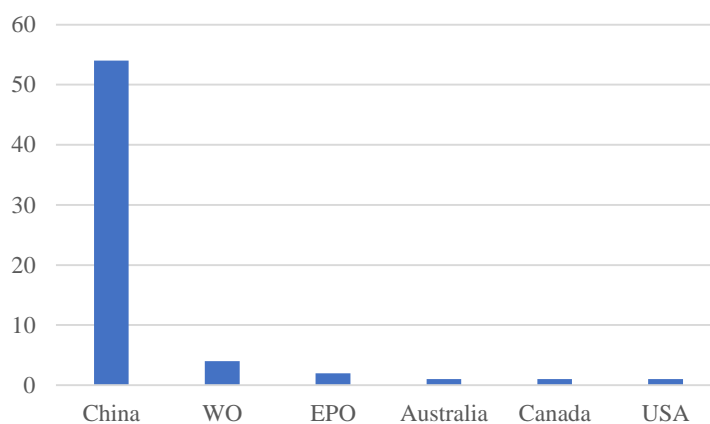
measure of similarity (ZUPIC; ČATER, 2015). As a result, it allows mapping and grouping the most important terms in the documents so that it is possible to present the knowledge base incorporated in the analyzed collection, in addition to exploring the different themes developed in the research domain (ARIA; CUCCURULLO, 2017; XIE, 2015).

In the collection of evaluated documents, genome editing, CRISPR, CRISPR/Cas9, Cas9, are the keywords that appear the most and are at the center of the network. There was the formation of 5 clusters (green, red, orange, blue, and purple). The purple (innovation and regulation) and orange (GMO - genetically modified organisms and new breeding techniques) clusters are composed of just two words and have weaker relationships, indicating that fewer publications explore these terms. These results are mostly related to publications regarding the current state of regulatory processes and technological development. Changes in policy and regulations are considered controversial in this matter and take several years (PURNHAGEN; WESSELER, 2020). Fewer publications in this area demonstrate the lack of equilibrium between science versus policy/lobby advances. The blue cluster also shows weak relations with the others - formed by the words plant breeding, biotechnology, and mutagenesis.

The red and green clusters are the ones with the most frequent words and are related to crops, such as maize, potato, tomato, rice, and soybean. Species for which there is a greater number of publications using the CRISPR technique. The terms gene targets, gene editing, and resistance are also present in these clusters, possibly due to the interest in using the CRISPR technique for the study of target genes, resistance to diseases and abiotic stress in plants (ARORA; NARULA, 2017; GIACOMELLI *et al.*, 2019; JAIN, 2015).

For patents, there was a total of 63 innovations registered for “plant breeding AND CRISPR” at the WIPO database. This database is a world reference source for intellectual property information. Amongst the results, most were related to patent deposits in China (Figure 5) and few others at the European Patent Office and Australian, Canadian, and North American offices.

Figure 5. Number of patents by the office of origin for the search term "plant breeding AND CRISPR". China, WO - granted by the World Intellectual Property Organization (WIPO), EPO – European Patent Office, Australia, Canada, and United States of America (USA).



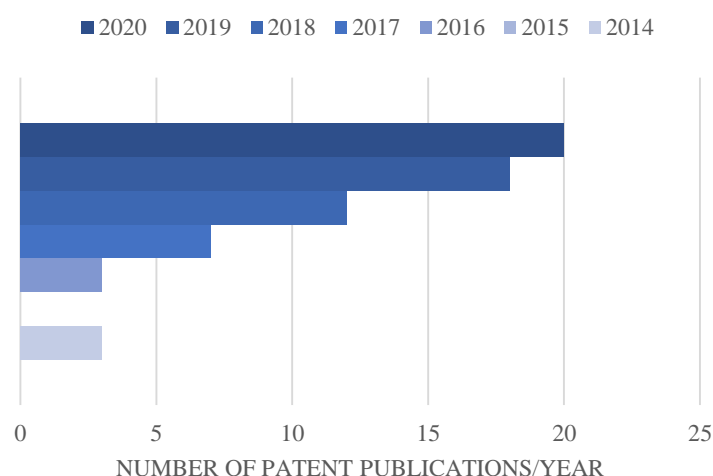
Source: Souza (2021)

The patents included innovations for tomato, alfalfa, mung bean, corn and, mostly rice (approximately 48%). Rice is one of the most important crops worldwide, a primary food source for more than half the world population. However, climate and production system changes have caused a reduction in rice fields' productivity. In contrast, the demand for this crop is expected to increase in the following decades, causing major rice consumer, China, to produce, import, and, mainly, invest in innovation to increase productivity (CHEN, C. *et al.*, 2020). A study has shown that government policies can induce investments in R&D in China. However, companies are already expecting regulatory changes in the next 5 years and have speculatively invested in new plant breeding technologies (DENG *et al.*, 2019).

It is noteworthy the annual increase in patents registered for plant breeding using CRISPR tools,

indicating growth in innovative events (Figure 6). Despite recent, with first studies published in 2013 (JIANG *et al.*, 2013), this technology has been applied to patented innovations the following year. This emphasizes the close relationship between scientific publications and patents for innovations in this field, indicating a more product-driven research. Studies compute a high number of filled patent requests under analysis by the same countries, such as 165 patent filings for China, for example (GUPTA *et al.*, 2020). It is also important to disclose that some patents might not be publicly available and under secrecy period guarantees.

Figure 6. Number of patents publications per year for the search term “plant breeding AND CRISPR”.

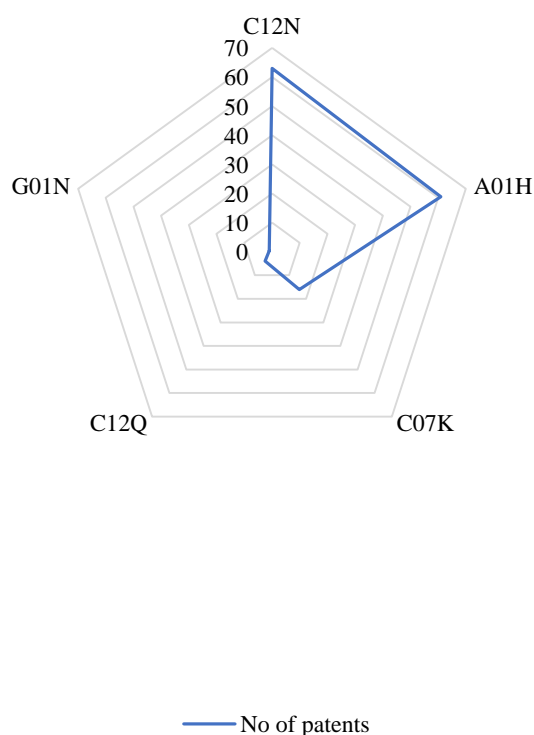


Source: Souza (2021)

The prospected patents are classified in five areas of the International Patent Classification (Figure 7). The innovations are related to “Microorganisms or enzymes; compositions thereof; propagating, preserving, or maintaining microorganisms; *mutation* or *genetic engineering*; culture media” (C12N) and “New plants processes for obtaining them; plant reproduction by tissue culture techniques” (A01H). Sixteen patents were also classified in “Peptides (peptides containing β -lactam rings C07D; cyclic dipeptides not having in their molecule any other peptide link than those which form their ring, e.g. piperazine-2,5-diones, C07D; ergot alkaloids of the cyclic peptide type C07D 519/02; single-cell proteins, enzymes C12N; genetic engineering processes for obtaining peptides” (C07K), a classification directly related to C12N due to the methods used in obtaining these peptides.

Figure 7. Number of patents per International Patent Classification (IPC) for the search term “plant

breeding AND CRISPR.



IPC	DESCRIPTION
C12N	Microorganisms or enzymes; compositions thereof; propagating, reserving, or maintaining microorganisms; mutation or genetic engineering; culture media.
A01H	New plant processes for obtaining them; plant reproduction by tissue culture techniques.
C07K	Peptides (peptides containing β -lactam rings C07D; cyclic dipeptides not having in their molecule any other peptide link than those which form their ring, e.g. piperazine-2,5-diones, C07D; ergot alkaloids of the cyclic peptide type C07D 519/02; single-cell proteins, enzymes C12N; genetic engineering processes for obtaining peptides.
C12Q	Measuring or testing processes involving enzymes, nucleic acids, or microorganisms (immunoassay G01N 33/53); compositions or test papers therefore; processes of preparing such compositions; condition-responsive control in microbiological or enzymological processes.
G01N	Investigating or analyzing materials by determining their chemical or physical properties (measuring or testing processes other than immunoassay, involving enzymes or microorganisms C12M, C12Q).

Source: Souza (2021).

Among the innovations created for plant breeding using CRISPR tools, applications were directed at abiotic stress tolerance, male-sterile plants, grain shape, metabolic alterations, and productivity. Most patents are targeted at inserting climate change adaptations to maintain/increase grain or green mass productivity through a molecular approach.

Future reviews may explore the compatibility of different CRISPR methods for agricultural solutions. The technique has evolved to include various methodological approaches involving, for instance, different associated proteins (Cas9, Cas12). Also, a distinction between research as a basis for marker-assisted selection in traditional plant breeding and research for the creation of GMOs might provide a better scenario on science versus regulatory processes.

5 CONCLUSION

Genome editing via CRISPR has been established as a tool of high relevance for biotechnology in less than a decade. There is a prospect for impactful growth in R&D in agriculture in the near term. Publications of articles and patents have increased exponentially for CRISPR-based solutions in plant breeding. Despite the highest number of publications, research has led to a considerable amount of patented innovations in a short timeframe. China has the lead in the development of this technology for plant breeding, and among cultivated crops, rice has been further studied. Regulatory hurdles and social concerns may restrain the use of this technology throughout the world, but its potential to increase productivity in crop plantations is well recognized. It is expected the expansion of CRISPR-based solutions to other plants. This study represents the current scenario and may be expanded in the future to support policymakers and R&D

investments.

ACKNOWLEDGMENT

The authors expressed their gratitude to the Federal University of Sergipe and CAPES for their research support.

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