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RESEARCH PAPERS

RNAi and *Bt* approaches to insect-pest control: analyses and perspectives on trends in global patent publications

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Highlights

- An overview of transgenic and non-transgenic approaches to insect control is reviewed;
- Losses of up to 40%/year in the production of major crops are caused by insects;
- Mapping the global patent landscape can provide access to key technological advances and bottlenecks;
- USA-based biotech companies were mostly more relevant patent applicants;
- Brazil ranked 6th (RNAi) and 4th (Bt) positions in the number of patents for transgenic technology.

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Bt toxins;
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dsRNA molecules;
Insect-pest management;
Filed patents;
Technological prospection.

Abstract: Insect-pests are a limiting factor in increasing agricultural production worldwide. Although major crops, including soybean (*Glycine max*), maize (*Zea mays*), and cotton (*Gossypium hirsutum*), face high pesticide costs in an attempt to mitigate or control pests, losses of up to 40% of production are recorded every year. In this scenario, transgenic crops remain one of the most promising biotechnological tools for reducing chemical pesticide costs. For instance, transgenic and non-transgenic technologies have been applied based on powerful approaches using double-stranded RNA (dsRNA) to silence essential genes of target insect-pests to silence them through RNA interference (RNAi) as well as *Bacillus thuringiensis* (*Bt*) toxins. Thus, patents using both dsRNA- and *Bt*-based technologies for insect-pest control in soybean, maize, and cotton crops were selected and evaluated in this study. We also compiled an updated list of countries and biotech companies that have filed patents using dsRNA or *Bt*-based technologies. We have used the World Intellectual Property Organization (WIPO) PatentScope international patent database to perform eight search strategies, using combinations of keywords and logical operators for patent search and retrieval. As a result, 93.9% of all selected patents were related to transgenic crops, whereas 6.1% were related to non-transgenic delivery approaches. Moreover, 51.2% of the patents described protection of *Bt* in transgenic crops, followed by 42.7% for RNAi in transgenic crops and 5.2% and 0.9% for non-transgenic *Bt* and RNAi technologies, respectively. Therefore, the current study attempts to promote innovative approaches based on existing and patented technologies to improve insect-pest control in crop plants.

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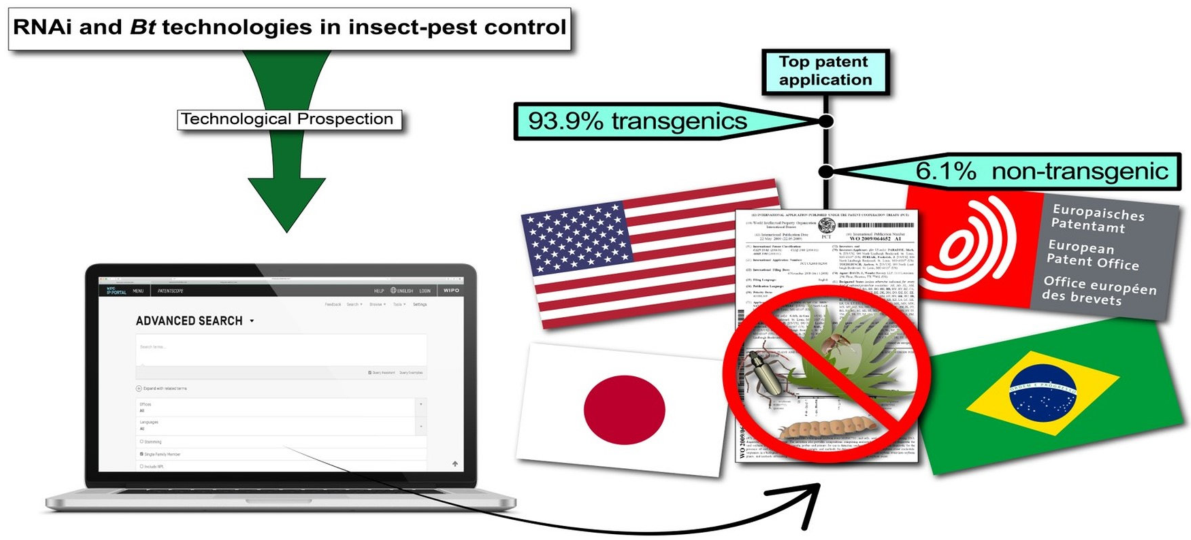
Graphical Abstract



Introduction

Insect-pest infestations continue to threaten agricultural productivity, causing annual losses of between 20% and 40% of global crop yields (Food and Agriculture Organization, 2022). However, chemical pesticides remain the most commonly used means of insect-pest control in the field, despite their potential to negative environmental and human health impacts (Cagliari et al., 2019), apart from the risk of target insects developing insecticide resistance (Katoch & Thakur, 2012, Khan et al., 2020). These impacts not only affect human health but also food security and are in conflict with the United Nations' Sustainable Development Goals (SDGs). Although climate change and the COVID-19 pandemic, and more recently the conflict in Ukraine, constricted availability and access to food, the harmfulness of pesticides to humans and food safety is considered a more pressing issue for further studies in developing countries (Sarkar et al., 2021). Therefore, large crop producers such as Brazil (which feeds over 800 million people worldwide) need to find innovative ways to increase crop productivity.

In this way, biotechnology has become the key to improving agriculture and reducing insect-pest damage by providing environmentally safe approaches, including the production of genetically modified (GM) crop varieties (Gebremichael et al., 2021). To put this in perspective, from 2019 (one year before the Covid-19 breakdown and before to the Ukraine conflict), consolidated data indicated that more than 18 million farmers in 29 countries grew transgenic crops with herbicide tolerance and/or insect-resistant traits, on a total of 190.4 million hectares (a ~112-fold increase since the first releases) (International Service for the Acquisition of Agri-biotech, 2019). In the last decade, GM crops have improved developing countries production by 22% and farmers' profits by 68% (Klümper & Qaim, 2014). Furthermore, GM crops resistant to pests have been produced through the modern agricultural biotechnology (Viktorov, 2019). Nontransformative *Bt*-approaches have also been developed for insect-pest control in the last decade, with successful results (Rao et al., 2018; Eski et al., 2019).

The use of toxins from gram-positive bacterium *Bacillus thurigiensis* (*Bt*), mainly crystal δ-endotoxin proteins (Cry toxins) with insecticidal activities, is a promising biotechnological approach to insect-pest control (Betz et al., 2000; Sanchis & Bourguet, 2009). After ingestion by the insect, the active and soluble Cry toxin binds to epithelial receptors in the insect gut, inserts into the target membrane, and forms pores that disrupt ion exchange and cause osmotic shock, resulting in cell lysis and insect death (Bravo et al., 2007; Sanchis & Bourguet, 2009; Pardo-López et al., 2013). Expression of *Bt*-based toxins has been found in both transgenic plants expressing Cry toxins (He et al., 2003; Du et al., 2014; Ribeiro et al., 2017, 2020) and in nontransformative *Bt*-based approaches (Sanchis & Bourguet, 2009; Kim & Je, 2012; Rodríguez et al., 2015; Rao et al., 2018; Eski et al., 2019). A promising alternative to *Bt*-based toxins is manipulating insect target genes via the RNA interference (RNAi) mechanism (Zhu & Palli, 2020). Hence, RNAi system is considered a reverse genetics tool as it has been used for functional gene analysis (Firmino et al., 2020; Jacques et al., 2020; Aklilu, 2021). RNAi is a specific post-transcriptional gene silencing mechanism in which RNA molecules recognize complementary RNA sequences of target genes (Cooper et al., 2019). Briefly, silencing induced by small interfering RNAs (siRNAs) occurs via an enzymatic complex called DICER, which cleaves long dsRNA molecules. Subsequently, it is incorporated into the Argonaute (Ago) complex that promotes target gene messenger RNA silencing (Katoch & Thakur, 2012; Kim et al., 2015). As the RNAi mechanism is conserved in eukaryotic organisms, it has been a widely-used approach for the development of transgenic plants expressing target genes that induce insect mortality or inactivity (Xiong et al., 2013; Gogoi et al., 2017; Dias et al., 2020; Jain et al., 2021). The efficiency of using dsRNA for insect-pest control depends on several factors, such as (i) the sensitivity of the insect to gene suppression by the RNAi system and; (ii) the method used for dsRNA delivery (Cooper et al., 2019, 2021). Recently, RNAi-based technologies have been used to develop new strategies for insect-pest control. The use of plant-mediated approaches for dsRNA expression in transgenic plants resulted in high levels of insect mortality has been the most suitable method for field application worldwide (Mao et al., 2011; Xiong et al., 2013; Han et al., 2017; Knorr et al., 2018; Wang et al., 2018; Ai et al., 2019). One of the most important advantages of using this technology is the fact that almost any lethal gene can be addressed for insect-pest control (Yan et al., 2021).

Due to the success of RNAi application against crop losses, non-transformative approaches have also been developed, including as foliar spraying, irrigation, and trunk injection (Palli, 2014; Zhang et al., 2015; Zheng et al., 2019; Gurusamy et al., 2020; Yan et al., 2021; Mishra et al., 2021; Yan et al., 2021). In controlled environments, non-transformative methods to deliver dsRNA molecules to the target insect-pest typically rely on microinjection and oral feeding (artificial diet) (Cagliari et al., 2019), but for obvious reasons, these methods are not practical for field applications. As insect nucleases can be a limiting factor (Garcia et al., 2017), nanoparticle-based delivery methods, such as chitosan and liposomes, have successfully improved the use of the RNAi system for insect-pest control once they can protect dsRNA molecules from enzymatic degradation (Lin et al., 2017; Castellanos et al., 2019; Chen et al., 2019; Zhu & Palli, 2020; Yan et al., 2021; Ribeiro et al., 2022).

Investment in technological innovation is essential to keep up with market developments. Due to the increase in patent applications, innovation and intellectual property (IP) have become important drivers of a country's economic development (Dutta et al., 2020). IP provides multiple benefits to individuals and organizations, as well as to farmers and consumers, by enabling the development of new insect-pest control tools (transgenic or non-transgenic) or options that provide improved traits desired by consumers (Lamberth et al., 2013; Sparks & Lorsbach, 2017). Generally, a transgenic elite event is protected by patents to obtain a new trait, which includes the expression cassette (promoter, target gene, terminator sequence, etc.), vectors, bacterial strains, and processes/protocols for plant transformation (Dunwell, 2005; Carroll, 2016). Furthermore, non-transgenic technologies can also be protected, including nanoparticles, bacteria expressing Cry toxins, and dsRNA for specific genes, stable dsRNAs processes, among others (Ghosh & Gundersen-Rindal, 2017; Cooper et al., 2021; Santos et al., 2021).

In this context, this study aimed to provide an overview of RNAi- and *Bt*-based technologies applied to insect-pest control that have been patented over the past 21 years. We focused on three major crop species (Viktorov, 2019): maize (*Zea mays*), cotton (*Gossypium hirsutum*), and soybean (*Glycine max*). Furthermore, we listed the top-ranked biotech companies/universities and countries involved in the development and application of intellectual property (IP) related to RNAi- or *Bt*-based tools useful for insect-pest control. Thus, the current study provides an overview of the available innovation trends that could serve as a useful resource for public and private institutions to improve crop insect-pests control. Therefore, the use of patent databases can be a productive means to obtain useful information and knowledge for universities, research centers, and biotech companies.

Methodology

Technological prospection was carried out using the World Intellectual Property Organization (WIPO) international patent database PatentScope (World Intellectual Property Organization, 2021a) with an advanced search. The search was performed in the "Front Page" field (criteria used to search the first page of the document - title, abstract, names, and numbers). Fields were also selected for topics related to the search term "Single Family Member", all "Offices" (covering over 50 countries and offices, e.g., Brazil, United States of America (USA), China, Argentina, European Patent Office (EPO)) and all "Languages". This approach brought back only one member of a patent family in all office's coverage of WIPO. PatentScope is a free patent search database providing access to the full-text of international Patent Cooperation Treaty (PCT) applications filed in many countries and different languages (World Intellectual Property Organization, 2021b).

The search was conducted in English and Portuguese, as Brazil is a leading grower of transgenic crops (International Service for the Acquisition of Agri-biotech, 2019). Several keyword combinations were tested, and eight search strategies and logical operators were defined when searching for patents on RNAi and *Bt* technologies applied to transgenic soybean, maize, and/or cotton and non-transgenic plants (Table 1). Moreover, the International Patent Classification (IPC) A01N was also included for non-transformative technologies to improve the research. This IPC brings results classified as biocides (pesticides and/or herbicides) and pest repellents or attractive, which were present in the documents related to the expected technology. All data from patent applications in both search languages were grouped for analysis. We identified patents related to the keywords in all available documents and all patent applications filed from 2000 to April 2021. Due to the large number of patents using the species "*B. thuringiensis*" species, we chose to include only the abbreviation (*Bt*) in the search. All collected data were manually organized in Excel® and SigmaPlot version 14.0 databases (SigmaPlot, 2017). For all plots and data related to the countries to which the patents belong, we use the "first priority country" option, i.e., the country where the patent was first filed and developed. The number of patent documents found across all search strategies is shown in Table 1.

Results and discussion

The development of biotechnological products for insect-pest control for field application depends on finding novel approaches and, most importantly, on knowing and using already available technologies. Herein, we provided an overview of the main investments in R&D and Innovation related to technology's communication and management challenges (Sørensen, 2011; Reyt & Wiesenfeld, 2015). Further surveys using the search for specific technologies can facilitate

Table 1. Search strategy used for patents on RNAi and *Bt* in transgenic and non-transgenic plants for insect-pest control in soybean, maize, and cotton (in English and Portuguese) and total number of patent applications from 2000 to 2021.

Language search	Main search	Patent database	Search strategy (Keywords)	Total entries
English	RNAi in TP	PatentScope WIPO	"transgenic plant*" AND (dsRNA OR RNAi) AND "insect pest*" AND (*Glycine max* OR soybean OR *Zea mays* OR maize OR *Gossypium hirsutum* OR cotton)	3399
	Bt in TP	PatentScope WIPO	"transgenic plant*" AND (Bt OR Cry) AND "insect pest*" AND (*Glycine max* OR soybean OR Zea mays OR maize OR *Gossypium hirsutum* OR cotton) AD:[01.01.2000 TO 07.04.2021]	4070
	RNAi in NTP	PatentScope WIPO	(dsRNA OR RNAi) AND "insect pest*" AND "plant*" AND (IC:A01N*) NOT transgenic AD:[01.01.2000 TO 07.04.2021]	74
	Bt in NTP	PatentScope WIPO	(Bt OR Cry) AND "insect pest*" AND "plant*" AND (IC:A01N*) NOT transgenic AD:[01.01.2000 TO 07.04.2021]	354
Portuguese	RNAi in TP	PatentScope WIPO	"planta* transgênica" AND (dsRNA OR RNAi) AND "inseto*" praga AND (*Glycine max* OR soja OR *Zea mays* OR milho OR *Gossypium hirsutum* OR algodão) AD:[01.01.2000 TO 07.04.2021]	19
	Bt in TP	PatentScope WIPO	"planta* transgênica" AND (Bt OR Cry) AND "inseto*" praga AND (*Glycine max* OR soja OR *Zea mays* OR milho OR *Gossypium hirsutum* OR algodão) AD:[01.01.2000 TO 07.04.2021]	25
	RNAi in NTP	PatentScope WIPO	(dsRNA OR RNAi) AND "inseto*" praga AND planta* AND (IC:A01N*) NOT transgênico AD:[01.01.2000 TO 07.04.2021]	2
	Bt in NTP	PatentScope WIPO	(Bt OR Cry) AND "inseto*" praga AND planta* AND (IC:A01N*) NOT transgênico AD:[01.01.2000 TO 07.04.2021]	62

Note: TP, transgenic plants; NTP, non-transgenic plants; IC, International classification; AD, Application date.

uncovering the development of inventive initiatives in each country (Ravaschio et al., 2010; Pereira & Quoniam, 2017).

In the current study, as an important first step, we have provided a comprehensive overview of the available innovative technologies (patent applications), their purpose, the main biotech companies, and the applicant countries, in order to pave the way for improving this demand in agriculture. Table 1 shows the number of patents found for both languages (English and Portuguese) for each search performed. A very small number (1.3%) of patent reports were found in Portuguese search, compared to the English search (98.7%). These results are to be expected as most patent documents are written in English, even if this is not the native language of the country of priority. Moreover, some patent documents in Portuguese contained keywords in English and/or similar terms in both languages, so the data were grouped to avoid errors in the final estimate of the number of patents. After grouping all the data, the results were as follows: 3,418 (42.7%) documents referred to patents using RNAi in transgenic plants (RNAi in TP); 4,095 (51.2%) patents were found describing transgenic plants containing *Bt* toxins (*Bt* in TP); 76 (0.9%) documents included RNAi in non-transgenic plants (RNAi in NTP), and 416 (5.2%) of them described *Bt* for non-transgenic plants.

Patents only measure the front-end of that process — the actual invention. This happens because patents describe the technology and/or aspects of product development only. Some patents (especially those describing new technologies with low TRL) even focus on the proof-of-concept or demonstration of a principle rather than prototyping and validating of new products. Therefore, patents do not necessarily measure the back-end of innovation - the launch of the commercialized product, which involves product and market development efforts. Although only part of all patents turns into a final product to the market, the increase in the number of patents over the last 20 years indicates a continuing interest by research institutes and biotech companies in finding new strategies to overcome crop losses due to insect-pest infestations. Moreover, with the increase in the world's population, all options for improving crop production must be explored. When applied alongside appropriate agricultural practices, insect-pest management can benefit farmers and consumers (Hurley & Mitchell, 2020; Tanda, 2022).

Main technological groups based on the IPC codes

In this study, an important point was identifying the IPC's main technological groups and subclasses. A comparison of the number of patent documents and their classification codes showed that, according to all searches, most patent documents were registered in the subclasses A01H (36.2%), C12N (33.4%), and A01N (8.5%) (Figure 1; Supplementary Material Table S1). Subclass A01H was represented in 99.8% of patent applications for RNAi and *Bt* using transgenic methods and in only 0.2% of patent applications for RNAi and *Bt* reolace in for using NTP. This subclass covers all aspects related to new plants, including disease resistance, cold resistance, and growth rate (World Intellectual Property Organization, 2021c), which explains its predominant use in patents for transgenic plants. The second-highest number of patents is represented by documents registered under classification code C12N, corresponding to 98.4% of patent applications on RNAi and *Bt* in TP and 1.6% of RNAi and *Bt* in NTP, indicating that these codes are more represented in patents related to transgenic plants. The subclass C12N focuses on patents related to recombinant DNA technology as methods for manipulating genetic material, including methods/procedures for producing, isolating, and purifying nucleic acids, and methods for introducing genetic material into microorganisms using vectors or other expression systems (Japan Patent Office, 2018). The third-largest subclass, A01N, followed the same trend as the previous codes: 64.8% of patents on RNAi and *Bt* in TP selected this code in their applications (Figure 1). These are patents mostly related to killing or preventing the growth or proliferation of undesirable organisms (e.g., insects, weeds, and microorganisms) (Japan Patent Office, 2018). Descriptions of other IPC subclasses found in all searches performed are provided in the supplementary material (Table S1).

The concentration of patent applications in first priority countries

The number of patent documents, ranked by first priority countries, was also evaluated (Figure 2). The results show that the United States of America (USA) has the most patent applications, including 3,239 patents (94.8%) for RNAi in TP; 3,799 patents (92.8%) for *Bt* in TP; 55 patents (72.4%) for RNAi in NTP; and 199 patents (47.8%) for *Bt* in NTP (Figure 2). Brazil ranked the 6th and 4th positions in the number of patents for RNAi (0.2% of patents) and *Bt* (0.5%) in TP, respectively (Figure 2A). For non-transgenic technologies, Brazil ranked the 5th and 3rd positions for RNAi (1.3%) and *Bt* (7.7%) technologies, respectively (Figure 2B). Interestingly, these results highlight that among the first priority countries (Figure 2B), Brazil stands out among developing countries and among the top producers of biotech crops (soybean, maize, and cotton). For example, the USA had the most approved transgenic events in 2019, and Brazil ranked 4th (International Service for the Acquisition of Agri-biotech, 2019). Notably, the USA and Brazil are among the 15 countries with the largest economies in 2021, ranking 1st and 11th, respectively (Cebr, 2022). The increase in the number of patent applications over the years is directly related to the expansion of biotech crop acreage through the immediate approval and commercialization of new traits, leading to a constant growth in crop production and improvement of their economies (International Service for the Acquisition of

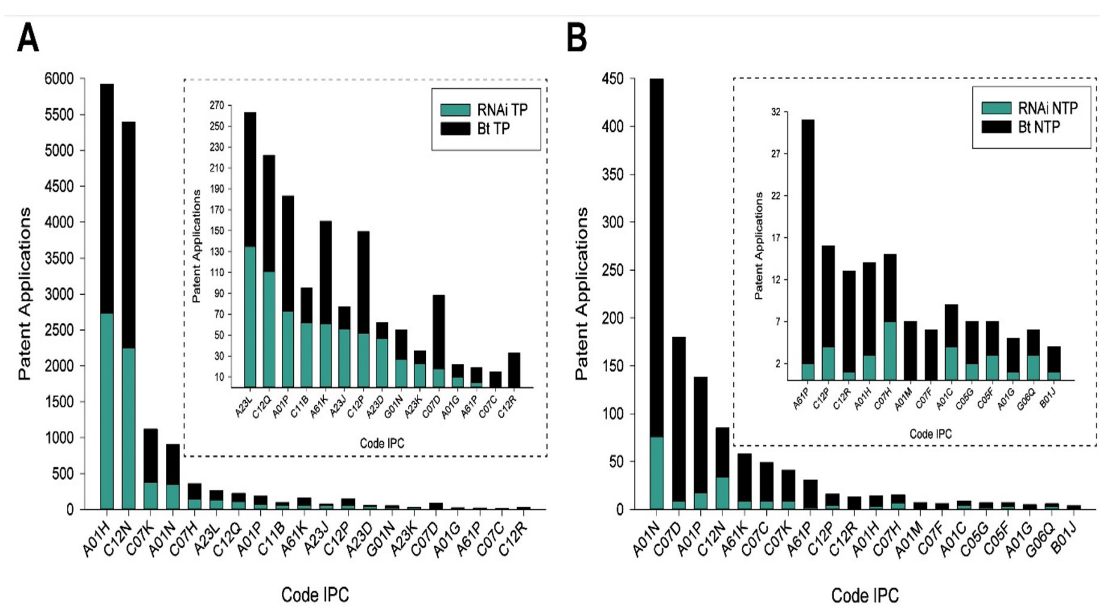
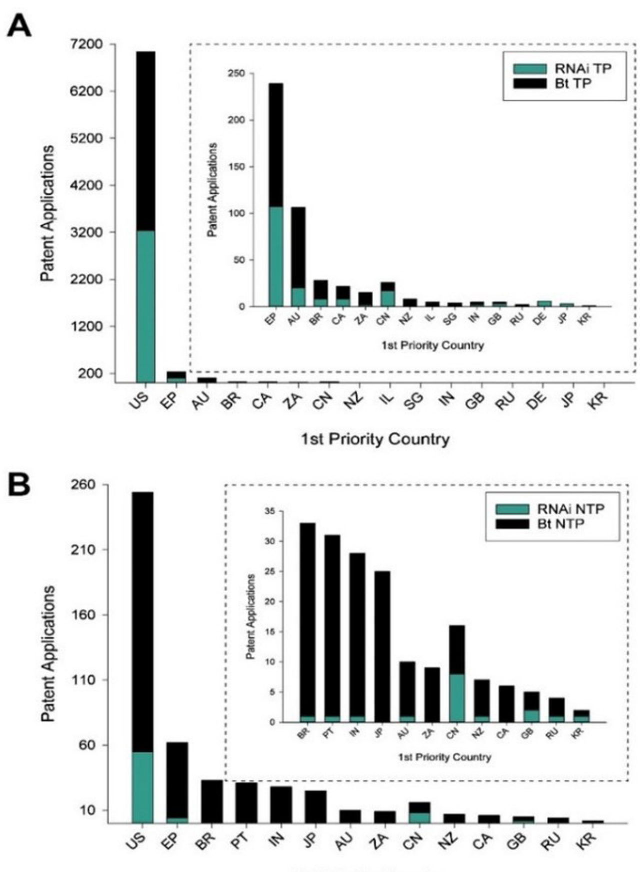


Figure 1. Number of patent applications according to the Top 20 International Patent Classification (IPC) subclass related to insect-pest control in crops based on the use of RNAi and *Bt* technologies for transgenic (A) and non-transgenic (B) plants, using data from PatentScope WIPO in the period from 2000 to 2021. RNAi in transgenic plants (RNAi TP); *Bt* in transgenic plants (Bt TP); RNAi in non-transgenic plants (RNAi NTP); *Bt* for non-transgenic plants (Bt NTP).

Agri-biotech, 2019). The USA has always been at the top of the list of countries filing the most patents, demonstrating its great capacity for technological development. Brazil, on the other hand, has a low number of patents filed, but shows a remarkable increase in technological development when compared to other developing countries, such as India (Figure 2).

Furthermore, our search for patents in Portuguese provided results for technologies that are protected exclusively in Brazil, even if they originated in other countries, such as the USA. Thus, it was found that there are countries interested in the development of transgenic and non-transgenic technologies for insect-pest control in Brazilian crops, including the USA, EPO, Japan, etc. In Brazil, the discussion on IP has gained prominence and is being held in different institutions to emphasize its importance and impact on the country's economy. Furthermore, Brazil is the second largest producer of transgenic crops in the world and has great technological investment potential (International Service for the Acquisition of Agri-biotech, 2019). Therefore, the increase in partnerships between universities and biotech companies could accelerate the development of commercial products and incentivize more patent applications.

However, nowadays, the major bottleneck in protecting the intellectual property of a product is the time it takes for a patent to expire. The commercialization timeline of a transgenic plant - from the development of the first transgenic lineage in the laboratory to the first commercial launch - is long (~15 years) (Rüdelsheim et al., 2018) and involves large investments (McDougall, 2011). The long time and high costs are mainly due to regulatory requirements and management expectations. Considering that the 20-year period for commercial exploitation of a patent starts from the day of its filing, what makes the innovation valid for patenting is a well-constructed protection that allows a better market position for their owners, adding value to the transgenic plant, as well as benefiting the holder of the rights in negotiations of licensing, assignment and technological co-development agreements. However, given that the protection strategies of a transgenic plant can be diverse, it is necessary that the agribusiness sector be always aware of current patents and registered cultivars, in order to anticipate possible obstacles in economic exploitation and infringements of IP rights (Colli, 2011). Therefore, patent holders from the USA, Canada, and Brazil are now facing the expiration of the first transgenic technology patents and are now on the run to submit new strategies to maintain the guarantee of protected traits (Rüdelsheim et al., 2018; Instituto Nacional da Propriedade Industrial, 2020).



Code	1st Priority Country
AU	Australia
BR	Brazil
CA	Canada
CN	China
DE	Germany
EP	European Patent Office
GB	United Kingdom
IL	Israel
IN	India
JP	Japan
KR	Korea (South)
NZ	New Zealand
PT	Portugal
RU	Russian Federation
SG	Singapore
TW	Taiwan
US	United States of America
ZA	South Africa

Figure 2. Distribution of patent applications by 1st priority country related to insect-pest control in crops, based on the use of RNAi and *Bt* technologies for transgenic (A) and non-transgenic (B) plants, using data from PatentScope WIPO for the period from 2000 to 2021. RNAi in transgenic plants (RNAi TP); *Bt* in transgenic plants (Bt TP); RNAi in non-transgenic plants (RNAi NTP); *Bt* for non-transgenic plants (Bt NTP).

These observations arouse our interest in analyzing the main government policies responsible for the changes in the countries that have filed the most patents in this field. In Brazil, the Innovation Law (Law No. 10,973/04) and Law No. 11,196/05 (Brasil, 2004, 2005) created effective policy incentives in the 2000s to encourage companies to develop Research, Development and Innovation (R&D&I) activities in the country through tax incentives for technological research and the development of technological innovations. Some recent studies on technological monitoring also show that the USA is the largest patent holder (Jalaluddin et al., 2019; Silva et al., 2020; Rodrigues-Silva et al., 2021a, b). USA is currently the largest economy in the world (Cebr, 2022), not only because of the resources investment in S&T and Innovation, but also because of other features of its innovation system. These include the close cooperation between universities, government agencies, and private biotech companies. In this field, the rules are very well established, including a comprehensive national patent system with fewer restrictions on patentability (Zucoloto & Freitas, 2013). The USA status as one of the top patent-filing countries could be explained by the innovation-related success of many USA agricultural and biotech companies (Table 2).

Notably, transgenic technologies, even though highly complex, benefit from decades of experience and clearer regulatory framework. Despite the low number of patent applications for non-transgenic RNAi and *Bt*-based technologies, our data show a continuous interest of both private and public sectors in developing such technologies over the years. As expected, more patents for new transgenic technologies are filed each year in countries where transgenic technologies are legal and where they hold leading market positions, such as the USA and Brazil, than in countries where legislation for transgenic technologies is less favourable. This is due to the fact that IP rights are central to the business and market strategies of biotechnology companies. It is therefore not surprising that biotech companies have become the largest contributors to IP, although this does not exclude the presence of universities and public research institutes.

Distribution of patents by applicants

Patent ownerships of *Bt* and RNAi technology for insect-pest control are distributed between academia, private and government companies. As shown in Table 2 and Table S2 (Supplementary Material), industries, including Monsanto, Dow Agrosciences, and BASF, owns many patent applications in this field. For instance, Monsanto was the main owner of patent applications for RNAi and *Bt* in TP, with 2,153 (52.8%) and 1,212 (25.4%) patents filed, respectively. For patent applications on RNAi and *Bt* using non-transgenic approaches, Dow AgroSciences - now Corteva Agriscience - (9 applications, 11.8%) and BASF (68, 16.3%) are the major players, respectively (Supplementary Material Table S2). According to the Global Innovation Index (GII) (Dutta et al., 2020, World Intellectual Property Organization, 2021), BASF and Monsanto were among the top 100 applicants in terms of patent innovation performance based on the GII metrics, ranking 53rd and 94th, respectively (Supplementary Material Table S2). For example, Monsanto has a technology that turned up in our searches and is already available as a commercial product (Paradise et al., 2009). This technology is a transgenic soybean event MON-877Ø1-2 (applied for in 2008, and registration number WO2009064652 (A1), which confers resistance to lepidopteran insects and is already approved for commercial use in several countries and regions, including Argentina, Brazil, Canada, China, the USA, Japan, and the European Union (Comissão Técnica Nacional de Biossegurança, 2021; International Service for the Acquisition of Agri-biotech, 2021). The transgenic event produces the toxin Cry1Ac, which acts by damaging the midgut lining of lepidopterans (Berman et al., 2009, 2011). Later, it was demonstrated that MON-877Ø1-2 soybean event was shown to have high potential for cultivation in the USA, Brazil, and Argentina, indicating that the transgenic crop could be used in fields with different climatic and geographical conditions (Berman et al., 2009, 2010, 2011).

It is noteworthy that Brazilian public and private institutions were also involved in patents related to *Bt* and RNAi technologies used for insect-pest control, such as EMBRAPA (Brazilian Agricultural Research Corporation), Catholic University of Brasilia (UCB), Federal University of Brasília (UnB), Federal University of Rio Grande do Sul (UFRGS), and others. For instance, 0.1% of all patents related to RNAi in TP were filed by EMBRAPA, as well as 0.4% of patents related to *Bt* in TP. Moreover, 0.7% of patents involving *Bt* in NTP technology were filed by Brazilian research institutes (Supplementary Material Table S2). The evaluation of the main patents filed in Brazil related to RNAi and *Bt* in TP showed that most of them were related to *Bt* technology (Table 3). Lepidoptera and Coleoptera are the main insect-pest classes targeted by these technologies. EMBRAPA and Pioneer Hi-Bred International Inc. stand out as companies with a high number of patent applications, indicating the interest in protecting insect-pest management technologies in Brazil (Table 3).

Table 2. Applicants with patents on RNAi and *Bt* using transgenic and non-transgenic approaches to insect-pest control in soybean, maize, and cotton - 2000 to 2021.

Applicants	RNAi in TP	*Bt* in TP	RNAi in NTP	*Bt* in NTP
Bayer	64	111	4	21
Dow AgroSciences	175	294	9	21
Monsanto	2153	1212	1	1
Syngenta	75	138	2	18

Note: TP, transgenic plants; NTP, non-transgenic plants.

Conclusions and perspectives

In the current study, we analyzed patent data filed over the past 21 years on transgenic and non-transgenic approaches used for insect-pest control in three major crop species (soybean, maize, and cotton). Data showed that most patents for transgenic products were for both RNAi- and *Bt*-based technologies. As expected, biotech companies made the largest contribution to IP, although this does not exclude the presence of universities. It is noteworthy that among the top patent applicants (companies and institutes), USA-based biotech companies were arguably more relevant, with a higher proportion of IP focused on transgenic plants development. The prominence of USA-based companies and the larger number of patent applications outside Brazil is not surprising. Although Brazil can be considered a scientific powerhouse (the country is regularly ranked features among the top 15 countries in the world in terms of scientific production - number of papers and citations), the Global Innovation Index ranks Brazil only 57th out of the 132 economies listed in the GII 2021. This indicates that while the country is capable

Table 3. Main Brazilian patent applications related to RNAi and *Bt* technologies in transgenic plants.

Patent application number	Application year	Event/Gene/Product/Process	Target insects	Owner
		RNAi technologies		
BR102012033506	2012	Silencing from gene *Laccase2*	*Anthonomus grandis*	EMBRAPA
		***Bt* technologies**		
BR102014003618	2014	Characterization of *Bt* Cry toxin Cry1B	*Sesamia inferens*	Beijing Dabeinong Technology Group Co., Ltd
BR102012033542	2012	Characterization of *Bt* toxin Cry1Ia12 and its mutants with improved toxicity	*Telchin licus licus*	EMBRAPA
PI0906128	2009	Characterization of new natural δ-endotoxins, mutant analogs, and synthetic analogs *Bt* Cry toxins, such as Cry8KaI and Cry8Ka5	*A. grandis*	EMBRAPA
PI0915049	2009	Characterization of a new *Bt* Cry toxin	*Ostrinia nubilalis, Papaipema nebris, Diatraea grandiosella, Spodoptera exigua, Plutella xylostella*	Pioneer Hi-Bred International, Inc.
PI0901169	2009	Characterization of *Bt* toxin Cry1Ac	*Anticarsia gemmatalis*	UFRGS
PI0720135	2007	Transgenic plants expressing CryI *Bt* toxins	*Helicorverpa zea, Heliothis virescens, S. exigua*	Pioneer Hi-Bred International, Inc.
PI0721812	2007	Characterization of *Bt* toxins	*O. nubilalis, H. zea, Agrotis ipsilon, S. frugiperda, Pseudoplusia includens, A. gemmatalis, Scirpophaga incertulas*	Pioneer Hi-Bred International, Inc.
PI0611681	2006	Characterization of the *Bt* toxin Cry8	*Diabrotica virgifera virgifera*	Pioneer Hi-Bred International, Inc.
PI0613111	2006	Characterization of *Bt* insecticidal proteins, S-layer proteins (ISLP)	Lepidoptera and Coleoptera	Universidad Nacional Autónoma de México
PI0508068	2005	Characterization of t *Bt* toxins Cry2Aa and Cry2Ab	Diptera and Lepidoptera	Pioneer Hi-Bred International, Inc.
PI0511868	2005	Characterization of a method for expressing the *Bt* toxin Cry2 in plastids using signal polypeptides	Insects	Pioneer Hi-Bred International, Inc.
PI0507893	2005	Characterization of lipase polypeptide having insecticidal activity in combination with *Bt* insecticidal proteins	*D. virgifera virgifera*	Pioneer Hi-Bred International, Inc.
PI0418365	2004	Characterization of *Bt* toxins Cry1, Cry3, Cry5, Cry8, and Cry9, with particular interest for Cry8 or Cry8-like	Lepidoptera	Pionner Hi-Bred International, Inc.
PI0418163	2004	Characterization of *Bt* Cry toxins Cry8-like and CryS-like and their variations, with optimized insecticidal activity	*Diabrotica* spp., *Leptinotarsa decemlineata, A. grandis*	Pioneer Hi-Bred International, Inc.

of generating new scientific knowledge, it has difficulty translating this into innovation. As a result, Brazilian industry tends to rely on foreign IP/technology (imported into the country) for new product development and release. This may explain the apparent discrepancy that the country is one of the largest producers of genetically modified crops in the world, and yet has a relatively low number of patent applications in this particular field.

As we have emphasized, mapping the patent landscape at a global and country level can help identify not only trends, key players and other market-related variables, but also provide access to technological efficiencies and key technological breakthroughs and bottlenecks. Future patents are likely to address technological innovations and capitalize on the global demand for effective and modern technologies to control agricultural insect-pests. Although significant progress has been made in these technologies (RNAi and *Bt*), as evidenced by the number of patents and patent applications issued over the past 21 years, the field of insect pest control continues to grow, with these technologies being applied to different insect pest species and crops. Based on the trends observed in our studies, we anticipate that both TP and NTP RNAi- and Bt-based technologies will expand rapidly in the coming years in response to the growing demand for effective and modern technologies to control agricultural insect-pests, enabling the rapid introduction of new varieties and/or formulations that will enable major agricultural nations to respond adequately to the growing global demand for food and bio-based agricultural products.

Conflict of interests

The authors declare that this work was conceived in absence of interest conflicts.

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Supplementary Material

Supplementary material accompanies this paper.

Table S1. International Patent Classification (IPC) subclasses are found in the search strategy.

Table S2. Total data and their percentages of patent applications related to insect-pest control in crops based on the use of RNAi and Bt technologies for transgenic and non-transgenic plants, using data from PatentScope WIPO (from 2000 to 2021) by applicants. RNAi in transgenic plants (RNAi TP); Bt in transgenic plants (Bt TP); RNAi in non-transgenic plants (RNAi NTP); Bt for non-transgenic plants (Bt NTP).

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