Latin America: A hub for agrobiotechnological innovations

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ABSTRACT

• **Background** Modern biotechnology is one of the last century's major advances in human science. Particularly in the agronomical field, the landscape of crop improvement technologies has witnessed a great expansion, driven by the integration of molecular and genetic engineering methodologies into the breeding toolbox. Latin America (LATAM) serves as a pioneering region in incorporating such techniques with several countries swiftly embracing these technologies.

• **Scope** This review aims to give a comprehensive overview of the elements that influenced agrobiotech acceptance in LATAM countries and how such cases could provide support for upcoming technologies to be considered worldwide.

• **Conclusions** Nearly 50 years of biotech breakthroughs have provided humankind with an impressive portfolio of tools already integrated into several life-sciences areas. The agronomical field has greatly progressed thanks to technologies derived from Genetically Modified Organisms (GMOs) and high promises are being made to also incorporate genome -editing products. LATAM's case is a prime example of how early introduction of novelties in the crop production chain can result in improved yields, paving the way for future developments to be easily integrated into the technological ecosystem of a region. The example set by LATAM can also be useful for the present gene-editing regulatory scenario. With several countries presently on the path to approving these methods in their current crop systems, basing their next steps on the southern continent's example, could represent a safe and practical pathway towards a new agronomical revolution.

Key words: Biotechnology, genetically modified organism (GMO), genome editing, transgenics, Latin America, adoption

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INTRODUCTION

Modern biotechnology is one of the last century's major advances in human science. In 1973, when Cohen described recombinant DNA, this milestone marked the birth of genetic engineering (GE) as a discipline (Cohen *et al.*, 1973). Since then, GE has evolved into a pivotal technology spanning diverse scientific domains. From biomedical advancements to industrial applications and agronomic innovations, GE has emerged as a transformative force. Particularly in the agronomical field, the landscape of crop improvement technologies has witnessed a great expansion, driven by the integration of molecular and GE methodologies into the breeding toolbox. This ranges from classical mutagenesis methods (Sikora *et al.*, 2011; Ma *et al.*, 2021), genotyping approaches using marker-assisted breeding (Collard *et al.*, 2008) to the use of genome-wide association studies (Huang *et al.*, 2014) and genomic selection (Crossa *et al.*, 2017) among others. The first development of genetically modified organisms (GMOs) in the 1980s (Van Larebeke *et al.*, 1974; Bevan *et al.*, 1983; Vaeck *et al.*, 1987) had a profound effect on modern agriculture. Headed by the obtention and testing of herbicide-resistant tobacco in fields in the USA and France (James *et al.*, 1996), GMOs brought a new era of (agro)biotechnological advancements. Nonetheless, GE also prompted governments worldwide to implement various regulatory schemes, primarily concerned with biosafety issues (Dale *et al.*, 1995). Globally, there are still different positions regarding their use: for some countries, the use of GMOs is perceived as a potential environmental and health threat. For others, it has become an important element in their economic development. This positioning regarding the technology has shaped the course of GMOs over the recent decades and now has a strong influence on the implementation of new breakthrough technologies such as genome editing (GEd) (Doudna *et al.*, 2014).

Latin America (LATAM) serves as a leading region regarding the regulation of GMOs. Several countries in the region have swiftly embraced this technology resulting in positive economic benefits for their producers and contributing to the country's economies through increased export activities related to international trade (Trigo, 2016; Brookes & Barfoot, 2020; Rodriguez *et al.*, 2021). However, this transition did not happen overnight, but is the result from a complex interplay of actors such as the establishment of regulatory agencies, the formulation of appropriate regulatory frameworks for GMOs, and the adoption of these products by their growers and consumer markets. More recently, the leading role LATAM countries played in establishing a regulatory framework for GEd technology has paved the way for its rapid incorporation into breeding programs. This review aims to give a comprehensive overview of the elements that influenced the adoption and acceptance of GMOs in most of the LATAM countries and how such cases could support GEd to be considered and adopted worldwide.

THE ONSET OF GMOs IN LATAM AND THE BIRTH OF REGULATORY FRAMEWORKS

The starting point of GMOs' introduction in the southern hemisphere can be traced back to Argentina (James *et al.*, 1996). In 1996, the country took the lead in adopting the technology in soybean (*Glycine max*) into its agricultural practices at an early stage closely following the United States (Trigo et al., 2003); being herbicide-tolerance (HT) the first trait incorporated (though technically the correct term should be "herbicide resistance," HT will be used in this manuscript to remain consistent with

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terminology used by the industry). One of the most important steps Argentina took in 1991 was the creation of a regulatory agency, the *Comisión Nacional Asesora de Biotecnología Agropecuaria* (National Advisory Commission on Agricultural Biotechnology, or CONABIA), which assisted in defining the risk assessment and approval processes for the cultivation, consumption and commercialization of GMOs and their products **(Fig. 1)**. Before, no country in the region had implemented such a protocol and this exemplary process served as the base for other regulatory frameworks in LATAM (Burachik *et al.*, 2002). Unlike conventional breeding products, GMOs' regulatory framework involves three independent evaluation instances for each product proposal to allow approval for commercialization of both external and locally developed traits (**Fig. 1**). On one side, an environmental risk assessment is performed by the Coordination of Innovation and Biotechnology (National Directorate of Bioeconomy) and CONABIA to ensure safety of the GMO release to the environment. Besides, the National Service for Agrifood Safety and Quality (SENASA) addresses animal feed and food safety evaluation through its Technical Advisory Committee on GMO Use (CTAUOGM). In addition, the Directorate of Agricultural Markets evaluates the GMOs' market impact. Once the three steps are accomplished, a decision regarding the approval of a Genetically modified (GM) event is issued by the Secretary of Bioeconomy. It is important to note that after the commercial approval of the GMO, a mandatory follow-up step is its registry in the National Seed Institute (INASE) (**Fig. 1**), whose role is not only the inscription of all commercial crop varieties (GM or not) in the country but also the certification of their distinctive traits. Registered varieties can be used for commercial planting and commercialization (**Fig. 1**).

Before the adoption of GM traits to soybean, this was still an emerging crop in LATAM and did not hold the significant economic role it plays today in the country (Trigo, 2011). Nowadays, HT soybean is intensively produced and the presence of an effective regulatory framework (alongside other elements) contributed considerably to the crop's acceptance by producers. One of these elements is that Argentina has a rich rural history and local farmers have always been eager to implement new technologies. By the 1990s, the country had already well-incorporated technologies from the "Green Revolution'', such as using high-yielding varieties, fertilizers, herbicides, and mechanization. Additionally, the local development of the no-till farming practices was a great innovation that revolutionized crop production (Peiretti *et al.*, 2014). As such, the arrival of a new promising technology was well received by the agricultural sector. Another important factor concerns the HT *per se*: farmers did not need to pay royalties for HT soybean, because the company that released it, Monsanto, had not applied for a patent on the trait in Argentina at the time (Qaim & Traxler, 2005). Moreover, glyphosate herbicide prices decreased, making the use of HT soybean much more profitable. Considering all the aforementioned points, by the year 1996, HT soybeans had already been approved and commercialized nearly simultaneously in both the USA and Argentina (James *et al.*, 1996). This was followed by a high adoption rate (defined as a high integration of the GMO traits in the local agronomical landscape and regular practices). Closely following this path, other important agronomical players in LATAM, like Brazil, Colombia and Uruguay, quickly implemented regulatory frameworks to regulate GMOs following this example. In addition, as CONABIA started performing evaluations aligning with the Cartagena Protocol on Biosafety (Eggers *et al.*,2000), it obtained consensus among countries worldwide that implemented the agreement's definitions in their regulatory evaluations (ISAAA, 2021). Recently, Argentina updated its regulatory policies on the environmental risk assessment, aiming to strengthen biosafety aspects. Among others, assessments of stacked GMO traits focusing on transgene interactions, insertion site effects and familiarity and history or safe use were taken into account in the procedure to further improve it (Vesprini *et al.*, 2022).

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Though the acceptance of GMOs rose fast in the region, not all countries devised completely unified criteria for them. In most cases, their use was fully or at least conditionally approved. In the cases of Brazil, Argentina, Colombia, Uruguay and Paraguay, their agencies' approval granted the full allowance for commercialization of GM crops for export and local use (Biotec-LATAM, 2024). Other countries though, like Chile or Costa Rica, only authorize confined activities with GMOs for research and development or to upscale seed for exports (Pacheco-Rodríguez *et al.*, 2014; Sánchez, 2020), but not for local consumption. Finally, some other members, like Bolivia, initially authorized their use but later on did not approve new traits due to internal concerns about the local diversity's germplasm protection. **Fig. 2** gives an overview of LATAM countries with established regulatory frameworks. By 2019, Argentina, Brazil, Paraguay, Colombia, Chile and Uruguay represented 44% of the area devoted to GM crops worldwide (ISAAA, 2019), consolidating the stand of LATAM as an important agrobiotechnological front.

GMO TECHNOLOGIES IN LATAM

LATAM plays a significant role in the commercial cultivation of biotech-derived crops worldwide. Brazil, Argentina, Paraguay, Uruguay and Bolivia account for nearly 80 million hectares covered by GMOs in 2019 and are among the top major commodities exporters (FAOSTAT). The main crops cultivated in LATAM countries include soybean, maize, wheat, cotton, as well as other contributing crops such as alfalfa, potato, sugarcane and beans. In the following section we will analyze case by case the main traits (both external and locally developed) incorporated in the region. Broadly, GMOs cultivated in LATAM can be classified in two main categories: first and second generation (Stegelin, 2011). The first generation primarily offers benefits to producers during the production phase (planting, crop management, etc) without directly altering the final product (**Table 1**). HT, insect and virus resistance are traits that fall under this category. In contrast, second-generation GMOs encompass traits that improve the final product itself, such as enhanced nutritional content or increased quality characteristics, which can vary widely among different species. A full summary of crops and traits produced per country can be found in **Fig.3.**

Soybean

The grain legume soybean is one of the most important crops sown in LATAM and is a major commodity of the region (Chang *et al.*, 2015). It is a primary source of vegetable oil and the beans' high protein content (40-42%) makes them an excellent option for animal feed and human food (Pagano *et al.*, 2016). Soybean was the first GM crop adopted in LATAM and presently represents the vast majority of the cultivated area of the region (FAOSTAT). Weed management is important in soybean production, because nearly 35% of the attainable product is estimated to be compromised by weed's competition in contrast to 16-18% by pathogens and animals (Oerke, 2006; Soltani *et al.*, 2017). Furthermore, it is also important for no-till farming systems, the preferred sowing method for soybean, as the procedure alters the weed populations' dynamics, favoring perennial species (Cordeau *et al.*, 2015). Consequently, the first wave of GM traits incorporated was HT, which helped standardize weed management. Among the most prominent ones stand glyphosate tolerance (Funke *et al.*, 2006), ammonium glufosinate resistance (van der Hoeven *et al.*, 1994); resistance to acetolactate synthase-inhibiting herbicides (Manabe *et al.*, 2007) and 2,4-D herbicide tolerance (Robinson *et al.*, 2015). Insect resistance (IR) traits were later

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introduced and engineered by overexpressing *Cry* genes encoding crystal proteins derived from *Bacillus thuringiensis* (Bt), which bind to midgut epithelial cells of sensitive insects leading to death (Bravo *et al.*, 2007). Stacking of *Cry* genes with herbicide tolerance was confirmed to provide both HT and IR to improve weed and insect management (Fast *et al.*, 2015). The fatty-acid composition was also an important trait for soybean improvement. Reduction of polyunsaturated soybean oil content in seeds has been achieved by silencing *GmFAD2* during the seed filling stage by means of overexpressing truncated forms of the gene (Knowlton, 1999) or by expressing double-stranded RNA targeting *FATB1a*, encoding a palmitoyl-acyl carrier protein thioesterase (EFSA Panel on Genetically Modified Organisms *et al.*, 2020). A major breakthrough in GMO development in LATAM was the first soybean drought tolerance (DT) variety obtained by overexpression of the *Hahb-4* gene, which encodes a *Helianthus annuus HomeoBox 4* transcription factor (HB4) (Dezar *et al.*, 2005a; Dezar *et al.*, 2005b). This variety was the first DT soybean ever tested, approved and commercialized (Waltz, 2015). *Hahb-4* has been reported to be induced by abscisic acid and ethylene and acts by modulating the plant's sensitivity to the latter (Manavella *et al.*, 2006; Manavella *et al.*, 2008). Transgenic lines expressing a copy of *Hahb-4* under the control of its own promoter demonstrated enhanced seed number production in 27 field experiments in warm and dry conditions (Ribichich *et al.*, 2020). Moreover, GM varieties were compositionally equivalent to their non-GM parental controls (Chiozza *et al.*, 2020). Recently, Plant Health Inspection Service (APHIS) of the US Department of Agriculture (USDA) granted Moolec Science SA, an Argentinian molecular farming food-ingredient company, the green light for its GM soybean expressing pig protein in their grains, which can be used for products with added organoleptic properties (APHIS, 2024).

Maize

Maize is the most produced staple crop worldwide and its history is intrinsically connected with LATAM´s countries in several aspects, ranging from commercial to cultural roles (Guzzon *et al.*, 2021). Being its birthplace and diversity center (Mexico particularly), the region is expected to produce more than 200 million metric tons by campaign 2024/2025 (USDA, 2024), being an important technological and agronomical hub. Maize HT and IR varieties were allowed for commercialization closely following soybean. They were rapidly incorporated into the agronomical local ecosystem, with more than 70 events (including single events and stacked traits) being approved (ISAAA GM Approval Database, 2024). For IR, several different types of Cry proteins (Palma *et al.*, 2014) have been used for insect management with high efficiency and without any effect over non-target invertebrates (Meissle *et al.*, 2022). Resistance evolution surged due to the IR technology requiring high-order stacks of Bt traits to confer increased protection (Gassmann *et al.*, 2011). The use of dsRNA as an alternative/reinforcement to Bt IR technologies has been recently approved in LATAM. The technology uses an dsRNA targeting the *Snf7* gene from *Diabrotica virgifera virgifera* (an important maize pest), which encodes a vacuolar sorting protein whose downregulation leads to corn rootworm lethality (Khajuria *et al.*, 2018).

Besides pathogen or weed control, other successful GM traits in maize include highly fermentable maize for ethanol and biofuel applications via the expression of a thermostable chimeric alpha-amylase gene (*amy797E*) (reviewed in Wolt *et al.*, 2007). Male sterility and fertility restoration methods are important traits desired in inbred maize lines to produce high-yield hybrids (Chen *et al.*, 2014). A system including the *ms45* fertility restoration gene and an alpha amylase enzyme (Wu *et al.*, 2016) has been approved

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for use in Brazil. The alpha amylase prevents starch accumulation in transgenic pollen grains, thus acting as an effective barrier for transgene flow.

Maize was also a pioneer crop in incorporating a DT trait, by constitutive expression of bacterial cold shock protein RNA chaperones (CSP), which enhanced seed yield when tested under water-limited conditions (Castiglioni *et al.*, 2008). This trait has only been approved for use in food and animal feed in Brazil (ISAAA).

Potato

Potato (*Solanum tuberosum L.*) has become one of the most widely cultivated food crops globally following its introduction from South America to Europe in the 16th century and subsequent expansion to various regions (Bradshaw *et al.*, 2009). In addition to its role as a significant source of carbohydrates in human diets, potato also holds a pivotal position in numerous industrial applications. Over one billion people worldwide consume potatoes, and the total global crop production exceeds 300 million metric tons (Campos *et al.*, 2020; FAOSTAT, 2024).

Potato production plays a vital role in global food security, but it faces significant hurdles from a range of biotic and abiotic stresses. Additionally, post-harvest storage presents challenges, like injury-induced enzymatic browning and the accumulation of reducing sugars during cold storage affecting tuber quality. The primary objectives of potato breeding programs are to sustainably increase yield and enhance tuber quality for both fresh consumption and industrial applications (Halterman *et al.*, 2016). However, improving potato tuber traits is complex due to the polyploid nature of potatoes and their predominant clonal propagation. GE technologies, such as transgenesis and GEd, offer promising solutions to tackle these obstacles, thereby contributing to food security and agricultural sustainability (Nahirñak *et al.*, 2022).

Genetically modified potatoes were among the earliest crops to be introduced, with the Russet Burbank variety incorporating the *CryIIIA* gene for resistance to the Colorado potato beetle, marketed commercially as NewLeafTM by Monsanto in 1995 (Perlak *et al.*, 1993). Subsequently, in 1998, Monsanto introduced NewLeaf PlusTM, another Russet Burbank variety resistant to both the Colorado potato beetle and potato leaf roll virus (Kaniewski *et al.*, 2004). NewLeafTM potatoes were approved for consumption as food in Mexico between the mid-1990s to early 2000s (not for cultivation) (ISAAA GM Approval Database, 2024). Despite their technological success and benefits for producers, consumers and the environment, anti-GMO activism regarding the safety of biotech food crops led to their market withdrawal in 2002 (Halterman *et al.*, 2016; Hameed *et al.*, 2018).

A potato virus Y (PVY)-resistant transgenic potato, SPT-TICAR, was entirely developed in Argentina by a research team from Instituto de Investigaciones en Ingeniería Genética y Biología Molecular (INGEBI-CONICET), collaborating with the company Tecnoplant-SIDUS. After introducing a transgene containing sequences corresponding to the PVY coat protein, more than 100 candidate lines were screened for PVY resistance in greenhouse conditions, leading to the identification of two genetically stable resistant lines, SY230 and SY233 (Bravo-Almonacid *et al.*, 2012). These lines were further evaluated in field trials across different potato-producing regions and growing seasons in Argentina, and no PVY infection was observed. The agronomic performance and biochemical composition of the selected lines demonstrated that they were substantially equivalent to the non-transformed Spunta variety (Bravo-Almonacid *et al.*,

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2012). After more than a decade of risk assessment by the Argentinean regulatory authority CONABIA, TIC-AR233-5 transgenic Spunta was approved for commercialization in 2015 (Ministry of Environment and Sustainable Development, 2020) and registered as a new potato variety SPT-TICAR at INASE in 2020.

Alfalfa

The legume alfalfa (*Medicago sativa*) is one of the most important crops used as forage to feed cattle (Ball *et al.*, 2001). It is a tetraploid legume cultivated primarily in Argentina due to its high nutritional value derived from its high protein content (Basigalup, 2007), making it an optimal feeding choice for meat and dairy production (Putnam *et al.*, 2001). The Monsanto - Forage Genetics consortium pioneered in the production and commercial release of glyphosate-tolerant alfalfa cultivars (alfalfa HT) in the USA in 2011. However, this release was preceded by more than five years of litigation between the biotechnology consortium and conventional alfalfa producers (Putnam *et al.*, 2001). Approval by the United States Supreme Court came with restrictions, including the obligation to maintain a minimum distance of 1000 meters between transgenic and conventional alfalfa crops.

Although alfalfa has emerged as a significant transgenic crop in the region, its adoption of transgenic technology is still limited compared to crops like soybean. In fact, despite the availability of these transgenic HT alfalfa materials since 2011, which entail significant economic yields, no transgenic varieties had been registered in LATAM until 2018. In Argentina, only three transgenic varieties of alfalfa are registered: WL 825 HVX.RR, WL 835 HVX.RR and WL 922 HVX.RR, commonly named HarvXtra® Alfalfa, developed by Forage Genetics International. The aforementioned varieties were submitted for registration with the INASE and are genetically modified to contain the events MON-00179-5 and MON-00101-8. These events confer tolerance to the herbicide glyphosate and a reduction in lignin content, derived from caffeic acid 3-*O*-methyltransferase (COMT) silencing (Guo *et al.*, 2001). This results in reduced lignin content in animal waste, leading to improved forage quality and greater efficiency in animal production. Notably, these three transgenic varieties are registered exclusively in Argentina and represent a very small percentage of the 468 alfalfa varieties currently registered in the region**.** However, its adoption by farmers is an ongoing process.

Wheat

Bread wheat (*Triticum aestivum L.*) is an allohexaploid species resulting from hybridization events involving three ancestral genomes (A, B, and D). Remarkably, its genome is estimated to be around ~17 Gb in size, with approximately 80% consisting of repetitive (non-coding) DNA sequences. This characteristic renders it one of crop species' largest and most intricate genomes (Arumuganathan *et al.*, 1991; The International Wheat Genome Sequencing Consortium, 2014; Uauy, 2017). With more than 770 million tons harvested worldwide, wheat is a fundamental component of human diets and a key crop for global food security, providing a substantial portion of the protein (25%) and calories (20%) consumed worldwide (FAOSTAT, 2024).

Wheat, one of the earliest cereals to be domesticated, originated in the fertile crescent around 10,000 years ago (Larson *et al.*, 2014). The Green Revolution of the 1970s, spearheaded by Dr. N.E. Borlaug and colleagues, dramatically enhanced agricultural productivity by introducing disease-resistant, semi-dwarf, high-yielding wheat cultivars (Venske *et al.*, 2019). Despite these initial successes, recent trends

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highlight the urgent need for further innovation. Exploring novel approaches, including genetic engineering, is imperative to sustainably enhance yield and nutritional quality .

The first report on successful wheat genetic transformation was published in 1992, incorporating the HT trait (Vasil *et al.*, 1992). Later, in 2004, approval was granted in the US, New Zealand, Australia and Colombia for the use as food of Roundup-Ready® Wheat, a transgenic wheat tolerant to the glyphosate herbicide (expressing the *cp4 epsps* gene from *Agrobacterium tumefaciens*), developed by Monsanto Company (Hu *et al.*, 2003). However, its commercialization never took place, likely due to resistance from wheat growers in the USA and Canada, who were concerned about the potential impact on international trade dynamics (Fox, 2009) among other factors. Wheat was even dubbed the "cereal abandoned by GM" (Wulff *et al.*, 2018).

Almost 20 years after the development of the first GM wheat, an Argentinean public/private alliance between the Instituto de Agrobiotecnología del Litoral (IAL-CONICET) and Bioceres S.A. succeeded in developing the DT transgenic wheat event IND-ØØ412-7, registered as HB4® wheat (Ayala *et al.*, 2019; González *et al.*, 2019). Transgenic event IND-ØØ412-7 obtained approval for commercial cultivation by the Argentinean regulatory authorities in 2020. However, it was not until Brazilian authorities granted the corresponding import approval that commercial cultivation in Argentina could begin (Brazil being the main export market for Argentine wheat). To date, HB4® wheat has been approved for cultivation in Argentina, Brazil and Paraguay, and for consumption as food and feed in Colombia, the US, Australia, New Zealand, Nigeria, South Africa, Indonesia and Thailand (Bioceres Crop Solutions, 2024; ISAAA, 2024).

Cotton

Cotton (*Gossypium hirsutum L.*) is one of LATAM's most important non-food crops primarily used in the textile industry. Cotton is the leading fiber crop and an important protein, oil, and pharmaceutical source. It has been cultivated in the region since pre-Columbian times. The major production is centered in Brazil, Argentina, Mexico and Peru, the latter being the origin of local varieties (Hoffmann *et al.*, 2020). As global warming and environmental changes continue, traditional cotton breeding techniques must be supplemented with new molecular tools to remain competitive against synthetic fiber. Although transgenic technology has enabled significant progress in breeding new cultivars with useful agronomic traits, the need remains for cotton to be more tolerant to numerous environmental extremes (Peng *et al.*, 2021). In Argentina, 14 transgenic cotton varieties have been registered, with the first dating back to 1998. These varieties exhibit different traits: six varieties confer resistance to Lepidopteran insects through the MON531 (Qaim *et al.*, 2003; Torres *et al.*, 2010). Additionally, two other ones exhibit tolerance to the herbicide glyphosate through the MON1445 event, with the initial registration in 2001 (Qaim *et al.*, 2003). Moreover, six stacked varieties have also been registered in the country.

The MON531 event provides resistance to Lepidopteran insects, such as certain moth and butterfly larvae, which can cause significant damage to cotton crops by feeding on leaves and buds. Introducing genes that confer resistance to these insects enables cotton plants to better defend against their attacks, thereby reducing yield losses and the need for chemical insecticides.

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On the other hand, the MON1445 event confers tolerance to the herbicide glyphosate, which simplifies weed management and can increase crop efficiency by reducing weed competition for nutrients and soil water. Since the approval of the first Bt cotton variety in 1998, adoption in several LATAM countries has been swift, with Brazil taking the lead (Libera *et al.*, 2016). Bt technology has been widely used to control pests like the bollworm and budworm, leading to increased productivity and reduced chemical insecticides use (Qaim *et al.*, 2003). Paraguay, Argentina and Colombia have also adopted transgenic cotton as well. As new technologies are introduced and their benefits demonstrated, adoption is expected to continue growing throughout the region (Rocha-Munive *et al.*, 2018).

Other relevant crops and technologies

Besides the aforementioned varieties and technologies mentioned, several traits for other relevant local crops have been developed and approved for commercialization in the region. Sugarcane (*Saccharum officinarum L.*) is an economically important crop in Brazil and Mexico (FAOSTAT, 2024) which proves challenging to improve through classical breeding methods due to the polyploid and hybrid genetics of elite cultivars (Healey *et al.*, 2024). As such, the introduction of traits through transformation represents a useful technology to bypass this limitation. Glyphosate and insect-resistant varieties have been developed successfully in Brazil and Argentina, displaying improved performance and equal biomass composition when compared to regular cultivars (Falco *et al.*, 2000; Noguera *et al.*, 2015; Gianotto *et al.*, 2019). However, the only genetically modified sugarcane approved for commercialization in LATAM is the insect-resistant sugarcane in Brazil. Common bean (*Phaseolus vulgaris*) is the most important grain legume for human consumption worldwide and a cornerstone in Brazil's social and agronomical landscape (de Faria *et al.*, 2013). Beans are particularly susceptible to several diseases that decrease its seed yield, especially viral pathogens (Tang *et al.*, 2023). By the introduction via transgenesis of an intron-hairpin genetic construct to induce post-transcriptional gene silencing of the *AC1* gene (necessary for virus replication) lines highly resistant to viral infection have been developed, subsequently increasing yield (Bonfim *et al.*, 2007; Souza *et al.*, 2018). The technology was completely developed by the Brazilian Agricultural Research Corporation (EMBRAPA) and later approved for commercialization in Brazil for some years now. Tree improvement has also been developed in LATAM. Eucalyptus (*Eucalyptus* spp.) overexpressing the *CEL1* gene, encoding a glucanase that promotes enhanced height plants with increased stem diameter and wood index (Shani *et al.*, 2004), has also received approval for commercial use in the region. Other approved traits and events include blue roses (*Rosa hybrida*) and Carnations (*Dianthus caryophyllus*), generated by overexpression of anthocyanin biosynthesis enzymes (Katsumoto *et al.*, 2007) and grown in Colombia, and glyphosate tolerance Canola (*Brassica napus)* in Chile (Biotec-LATAM 2024). Safflower (*Carthamus tinctorius*) overexpressing chysmosin, an enzyme used for milk coagulation in cheese preparation, is grown for commercial use in Argentina (reviewed in Bravo-Almonacid *et al.*, 2016). Another interesting product is Pinkglow™, a unique variety of GM pineapple (*Ananas comosus*) that has a vibrant pink flesh and delayed senescence. Developed by Del Monte Fresh Produce, Pinkglow™ pineapples are cultivated in Costa Rica, but approval for consumption was only granted in the USA and Canada (Lobato-Gómez *et al.*, 2021). For the increased lycopene trait, the developer introduced the phytoene synthase (*Psy*) gene from tangerine (*Citrus reticulata*) and used the RNA interference (RNAi) technology to suppress the expression of endogenous lycopene β-cyclase (*bLyc*) and lycopene ϵ-cyclase (*eLyc*) genes. Additionally, to regulate flowering and achieve delayed senescence,

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Del Monte Fresh Produce targeted the expression of the endogenous meristem-specific *ACC synthase* gene using RNAi.

REGULATORY FRAMEWORK FOR GEd CROPS IN LATAM

Following the thrive of transgenics in the 90s -2000s, a subset of molecular techniques involving site-directed nucleases (SDNs) were in development (Podevin *et al.*, 2013). SDNs allowed targeted DNA mutagenesis by introducing strand breaks at specific genomic positions. By exploiting the different pathways of the cell DNA repair machinery, the results of its use could lead to random mutations, ranging from loss or gain of some nucleotides to large indels without any foreign DNA insertion (SDN-1 techniques). They can also be used to recombine foreign donor DNA with endogenous DNA by homologous recombination (SDN-2 techniques) and to directly insert DNA fragments at a defined locus using donor DNA (SDN-3 techniques). Since its beginning, the GEd technology mediated by SDNs has progressed through three primary generations of techniques: zinc-finger nucleases (ZFNs), transcription activator-like effector nucleases (TALENs), and more recently, clustered regularly interspaced short palindromic repeats (CRISPR) coupled with the CRISPR-associated protein (Cas) (Gaj *et al.*, 2013). This latter has been successfully engineered into an efficient and programmable system by the collaborative work of Jeniffer Doudna and Emanuelle Charpentier groups (Jinek *et al.*, 2012). Unlike ZFNs and TALENs, which rely on proteins to target DNA strands, CRISPR technology employs a Cas9 nuclease guided to its target sequence by a small segment of guide RNA (gRNA). CRISPR/Cas has since proven highly efficient and accessible, facilitating site-directed mutagenesis in various organisms, including plants (Lowder *et al.*, 2015), and ushering in a new era for SDNs. Diverging themselves from GMOs, the products derived from SDNs lead to another regulatory scenario that should and is being contemplated worldwide (Breyer *et al.*, 2009; Waltz, 2012). The USA early-on determined that products derived from such techniques would not be treated as GMOs (Waltz, 2012) and later exempted outcomes of SDN-1 and SDN-2 from regulation. In the case of Europe, SDNs were clustered alongside other techniques into the so-called New Breeding Techniques (NBTs), an initiative from the joint research center of the European commission to differentiate them from GMOs (Lusser *et al.*, 2011). Although the products obtained via NBTs are considered to date as GMOs, thus-requiring a previous authorization before commercialization (Eriksson *et al.*, 2019), its regulation is presently being reconsidered in this continent. After its departure from the European Union, the United Kingdom relaxed regulations concerning GEd considering them different from GMOs and releasing them from risk assessment when applying for crop cultivation (Wang *et al.*, 2023).

Considering its background with GMOs, Argentina was the first country to revise their regulatory framework for NBTs. The Argentinean government issued resolution 173 in 2015 to evaluate GEd crops and whether they would be classified under GMO regulation (Whelan *et al.*, 2015; Lema, 2019). The procedure performs a case-by-case evaluation of a postulated edited organism and determines if it falls under transgenic regulation based on the changes introduced in the genome **(Fig. 1)**. The assessment includes a full description of which GEd technique was used, the follow-up breeding process (if any) and proof of lack of transgene components (if applicable) (Lema, 2019). Products classified as possessing "new combinations of genetic material" (in concordance with the Cartagena Protocol on Biosafety, Eggers *et al.* (2000)) fall under GMO regulation. On the other hand, cases that do not involve the incorporation of genetic material (SDN-1 and SDN-2 techniques) are considered conventional products and are not regulated as GMOs (Goberna *et al.*, 2022). The new framework also provides the advantage

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of performing a “Prior Consultation Instance” to check if a future GEd plant still at “design stage” will meet the non-regulation criteria (Whelan *et al.*, 2015). Notably, the categorization is based on the fact that new genetic material is present in the plant and not on the technique used to develop it, contrary to European Union regulation (Eriksson *et al.*, 2019). This criterion facilitates any future NBT methodology to be covered by present regulation (Whelan *et al.*, 2015). Moreover, CONABIA earned the title of “reference center of biosafety” (FAO, 2023), providing assistance and counseling to other LATAM countries on how to evaluate the regulation of NBTs. Presently in LATAM, ten countries (Argentina, Brazil, Chile, Colombia, Costa Rica, Ecuador, Paraguay, Honduras, El Salvador and Guatemala) have established a regulatory framework following the aforementioned case example described (Gatica-Arias, 2020; Fernández Ríos *et al.*, 2024).

GEd TECHNOLOGIES IN LATAM

Research institutions and companies are rapidly embracing GEd technology in LATAM. The presence of an established framework has allowed different sectors to focus their research on the development of GEd traits with good perspectives to reach markets. Also, the incorporation of foreign-developed traits into the local market is ongoing. Furthermore, a more diverse roster of actors has been able to access the technology and potentially register new products, which in the case of GM crops was discouraged due to the extremely high costs associated with the regulatory process required for their approval (Goberna *et al.*, 2022). Large-scale GEd research projects involving several countries are also actively under development, evidencing the strong emphasis the region is putting on the technology (FONTAGRO; PROCISUR). Access to accurate information is complicated by the caution in communicating developments due to uncertainty regarding the adoption of GEd developments by certain international markets.

GEd has proven to be efficient in crops when the target trait can be achieved through knockout resulting from indels produced by the non-homologous end-joining mechanism. Consequently, it is not surprising that most advanced traits obtained through GEd involve loss-of-function effects. With the first GEd high-oleic oil soybeans hitting USA markets in 2019 (Knowlton, 2022), the development of edited traits for this legume is on the rise. Brazilian scientists have developed efficient stable systems for simplex and multiplex GEd in soybean (Carrijo *et al.*, 2021) and transient expression methods to test for gRNA efficiency (Koltun *et al.*, 2023). EMBRAPA has been applying GEd in different crops besides soybean such as sugarcane, maize and common beans, to improve nutritional and industrial quality and increase DT. To date, at least three edited lines have already been evaluated by the Brazilian National Technical Biosafety Commission (CTNBio), two soybeans, one edited to improve nutritional quality and another for increasing DT, and one sugarcane edited for increasing biomass digestibility (Polo, 2022). Potato breeding has not been an exception to incorporate GEd technology (for reviews, see Nadakuduti *et al.*, 2018; Nahirñak *et al.*, 2022; Chincinska *et al.*, 2023). Unlike seed-producing species where editing components (nucleases and guides) can be segregated (Bottero *et al.*, 2021), eliminating transgenes through crossing or self-crossing is not suitable for vegetatively propagated and highly heterozygous crops like potatoes. This limitation was overcome by transiently expressing editing machinery as ribonucleoproteins to generate the desired edits without integrating the CRISPR system. Traits of interest for GEd in potato include the inhibition of browning, reduction of cold-induced reducing sugars formation, starch modification and enhancement of resistance to biotic stresses, among others (for examples, see Andersson *et al.*, 2018; Hameed *et al.*, 2018; Nadakuduti *et al.*, 2018; Nahirñak *et al.*,

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2022). GEd potatoes are currently not available for cultivation or consumption in LATAM, but research laboratories in the region are actively working on advancements in this field. An example are potatoes with reduced enzymatic browning in tubers after editing the *StPPO2* gene in the tetraploid cultivar Desiree developed at Instituto Nacional de Tecnología Agropecuaria (INTA - EEA Balcarce, Argentina) (González *et al.*, 2020).

GEd has also opened exciting opportunities to improve wheat traits. Traits of interest for gene editing in wheat include yield enhancement, improvement of grain quality, biofortification, development of resistance against diseases and tolerance against abiotic factors (Nigro *et al.*, 2024). GEd also opens new doors for alfalfa forage enhancement. Several laboratories worldwide have successfully tested the method in this legume (Gao *et al.*, 2018; Chen *et al.*, 2020; Bottero *et al.*, 2021; Stritzler *et al.*, 2022). Particularly in LATAM, studies have focused on genes related to biological nitrogen fixation (Frare *et al.*, 2022), HT (Bottero *et al.*, 2022) and quality improvement (Galindo-Sotomonte *et al.*, 2023). In fact, the FAO has mentioned this latest development as an ongoing project utilizing CRISPR-Cas9 technology: alfalfa with enhanced quality and productivity (FAO, 2023). Regarding vegetable crops, significant advancements have been made by INTA with GEd in lettuce. A line has been created that exhibits delayed flowering and a notable increase in biomass. This effect was achieved via the knockout of the *Ls SQUAMOSA PROMOTER LIKE 13* (*SPL13*) gene, which is involved in plant phase transition and flowering induction in lettuce (Beracochea *et al.*, 2023).

Although GEd recent advances in LATAM look promising, several technical limitations can delay their incorporation into a commercial pipeline. Incorporation of a GEd trait directly in an elite cultivar can only be done if such line is transformation-prone, which is a common bottleneck for several crops (Chen *et al.*, 2022). Consequently, GEd trait introgression into elite lines follow the same pipeline than landrace-derived positive traits or even GMs, which normally are developed in transformable, non-elite cultivars (Glenn *et al.*, 2017). Furthermore, contrary to transgenic traits which are frequently dominant, GEd are commonly recessive or even require the simultaneous editing of several orthologs to bypass redundancy (Iohannes & Jackson, 2023). Thus, their introduction into elite germlines can take much more time and cost than with some GMOs traits (Ayub *et al.*, 2023).

DISCUSSION AND PERSPECTIVES

Nearly 50 years of biotech breakthroughs have provided humanity with an impressive portfolio of tools already integrated in several life-sciences areas. The agronomical field has greatly evolved thanks to technologies derived from the use of GMO and high promises have been made to incorporate GEd products. LATAM's case is a prime example of how early innovations in the crop value chain can result not only in higher yields, but also in better product quality and management. Moreover, such an initiative also paves the way for future developments to be easily integrated into a region's technological ecosystem. It also highlights the value of setting standardized and science-based criteria to evaluate technologies, with vanguard countries acting as reference points for follow-ups, assisting in streamlining regulatory procedures. In a broader sense, the technological package offered by GM and GEd can be viewed as a toolbox with potential to be used for various, and even similar, purposes. While some tools provide comprehensive solutions, other approaches may benefit from a combination of

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strategies. Resistant pests can be better managed by properly stacking the traits, or in the future, by integrating different technologies). This suggests a potential direction for agrobiotech in addressing the complex climate scenario. However, as with any toolbox, proper use of these technologies, coupled with responsible crop management practices, is crucial.

However, for countries worldwide to benefit from agricultural biotechnological advances, several steps must be taken, both scientifically and at the societal level. Pursuing science-driven policies to incorporate and facilitate novel methods in plant breeding is a first step in this regard (Dima et al., 2023). Awareness of the dangers of rapid climate change should also be coupled with insights into how biotechnology can lead to improved crops much faster than through classical methods. Another crucial aspect is public perception. With a history of 28 years of use, the food and environmental safety of GM crops has been thoroughly demonstrated (Goodman, 2024). Nonetheless, a percentage of people still reject their use (Funk et al., 2015). This aspect is likely derived from a lack of knowledge of the collective positive evidence. Better awareness campaigns and outreach sessions could greatly dispel common doubts about these technologies' uses and safety. GEd campaigns have generated a greater acceptance (McFadden et al., 2024). It is important to remark that although some countries have a restricted view of GM and GEd plants, this does not reflect the positions of their respective scientific sectors. Several major traits have been proficiently developed in regions where the products are banned, but commercialized in other countries whose regulatory frameworks allow a proper analysis and de-regulation. Recently, an open letter, including many Nobel laureates and scientists, urged European parliament members to reconsider their position regarding GEd in the face of the present climate scenario (WePlanet, 2024).

The example set by LATAM can also be useful for the recent GEd regulatory scenario. Several regions, including the United Kingdom, are on their way to develop a suitable regulation. As a result, they would need to define clear procedures to analyze products derived from these technologies. Funding stones, like the early conception of regulatory agencies, will greatly help streamline the technology evaluation process. By establishing a clear, simple and science-based procedure for analysis like those of Brazil, Argentina or the model set by the US, the market of GEd-derived products may soon globalize.

Finally, for LATAM and other countries that have already developed regulatory frameworks for GEd, the challenge lays in how to avoid a three type categorization (conventional, GMO and GEd), which may ultimately result in an overregulation of the GEd products and potential trade issues at a global level. This latter point will soon be tackled once GEd traits are established in regional markets and start coexisting with GMOs as different options for producers.

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FIGURE LEGENDS

Fig. 1: Regulatory scheme for new varieties in Argentina. Breeding products are characterized based on the technology used for their development such as conventional breeding (lower pathway), transgenic events (middle pathway) and NBTs (upper pathway). Depending on each type, particular evaluations are requested to allow the product to be commercialized. Approved products are then registered in the National Cultivar Registry (RNC) and then can proceed to commercial production. Source: CONABIA (2024).

Fig. 2: Current GMO policy in LATAM countries that grow GM crops. Sources: Biotec-LATAM (2024).

Fig. 3: GMO traits approved and commercialized in LATAM classified by country and crop. Sources: Biotec-LATAM (2024); ISAAA GM Approval Database (2024).

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TABLES

Table 1: GMO developments in LATAM based on the trait, the generation and the Origin of development.

Crop	Trait	Generation	Origin of Development
Soybean	Hebicide tolerance	First	Multinational
	Insect resistance	First	Multinational
	Drought tolerance	Second	LATAM - Argentina
Maize	Hebicide tolerance	First	Multinational
	Insect resistance	First	Multinational
Cotton	Hebicide tolerance	First	Multinational
	Insect resistance	First	Multinational
Wheat	Drought tolerance	Second	LATAM - Argentina
Alfalfa	Hebicide tolerance	First	Multinational
	Low lignin	Second	Multinational
Canola	Hebicide tolerance	First	Multinational
Sugarcane	Insect resistance	First	LATAM - Brazil
Bean	Virus resistance	First	LATAM - Brazil
Potato	Virus resistance	First	LATAM - Argentina
Pineapple	High lycopene content	Second	Multinational
Carnation	Blue flowers	Second	Multinational
Rose	Blue flowers	Second	Multinational
Safflower	Chymosin expression	Second	LATAM - Argentina

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Figure 1

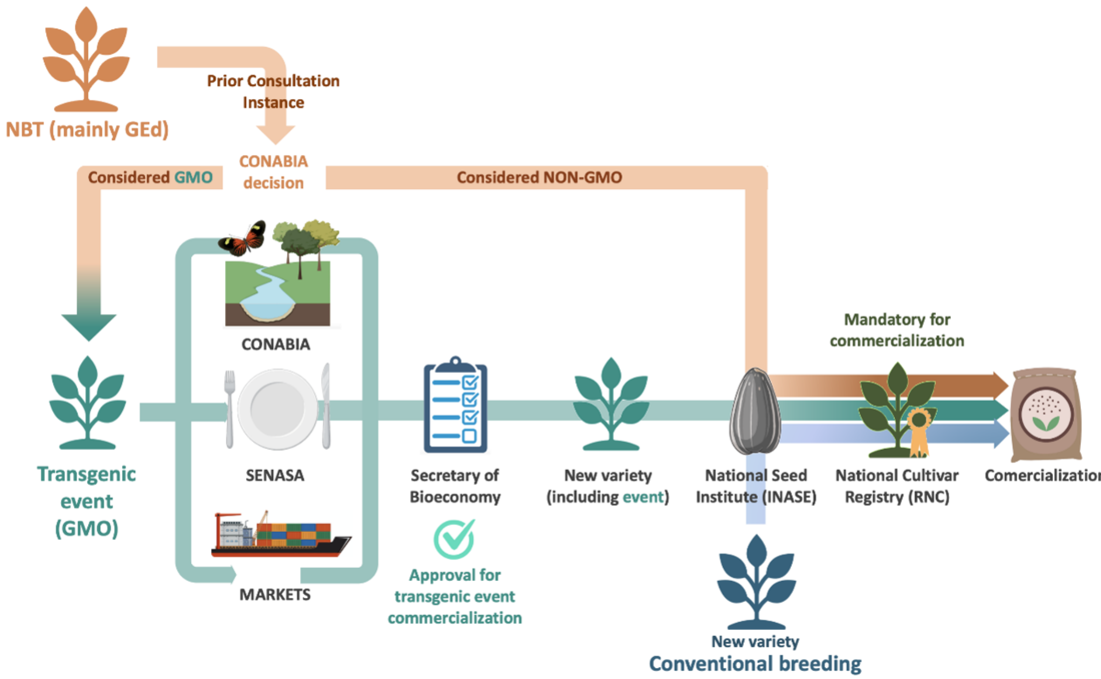

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Figure 2

Country	Regulatory Framework (RF) Reference Entities	RF Since (Year)	GM crop planting	Area with GM crops* (ha)	Type of authorization for GM crops
Argentina	National assesment comission of agricultural biotechnology (CONABIA)	1991	Yes	23,500,000	Commercial cultivation, field trial and contained acitivities
Bolivia	National Committee on Biosafety and the Biosafety Regulation	1997	Yes	1,400,000	Commercial cultivation, field trial and contained acitivities
Brazil	Brazilian National Biosafety Technical Commission (CTNBio)	1995	Yes	63,200,000	Commercial cultivation, field trial and contained acitivities
Chile	Agriculture and Livestock Service (SAG)	1992	Yes	10,000	Import and GM crops planting for production of seed for exports.
Colombia	Ministry of Agriculture and Rural Development	1996	Yes	100,000	Commercial cultivation, field trial and contained acitivities
Costa Rica	Ministry of Agriculture and Livestock	1991	Yes	212	Import and GM crops planting for production of seed and/or niche market food products for exports.
Cuba	Ministerio de Ciencia, Tecnología y Medio Ambiente (CITMA)	1999	Yes	500	Recently started cultivating a locally developed GM maize
Dominican Republic	Ministry of Environment and Natural Resources (MIMARENA)	2015	No	NA	There is no approval process for GE events, nor authorization for commercial or field trial planting
Ecuador	National Biosafety Committee	2017	No	NA	Ecuador's 2008 Constitution declares the country to be free of GM crops and sedes. Exception in case of national interest
El Salvador	Ministry of Environment	2018	No	NA	RF exists but norms still required; no authorizations for GM crops cultivation or export granted so far
Guatemala	Ministry of Agriculture, Livestock and Food (MAGA)	2019	No	NA	Import and GM crops planting for production of seed for exports.
Honduras	National Service for Agrifood Health and Safety (SENASA)	1998	Yes	100,000	Commercial cultivation, field trial and contained acitivities
Mexico	Inter-secretarial Commission on GMO Biosafety	1995	Yes	20,000	Commercial cultivation ongoing (not GM maize) but not granting authorization for new GMO crops
Nicaragua	Commission of Risk Analysis of Living Modified Crops (CONARGEM)	1999	No	NA	Not granting authorizations for GMO
Panamá	National Biotechnology Commission (CNB)	2002	No	NA	Commercial cultivation, field trial and contained acitivities
Paraguay	National Agricultural and Forestry Biosafety Commission (CONBIO)	2004	Yes	3,700,000	Commercial cultivation, field trial and contained acitivities
Peru	National Institute for Agriculture Innovation	1999	No	NA	An active moratorium does not allow the approval of GMOs
Uruguay	National Biosafety System (SNB)	1996	Yes	1,200,000	Commercial cultivation, field trial and contained acitivities
Venezuela	Ministry of Eco-Socialism (MINEC)	NA	No	NA	Seeds Law prohibits production, import, use, multiplication and introduction of GM seeds into the country

* Area reported for 2022, except for Costa Rica, corresponding to 2019 value, and Cuba corresponding to 2020 value.

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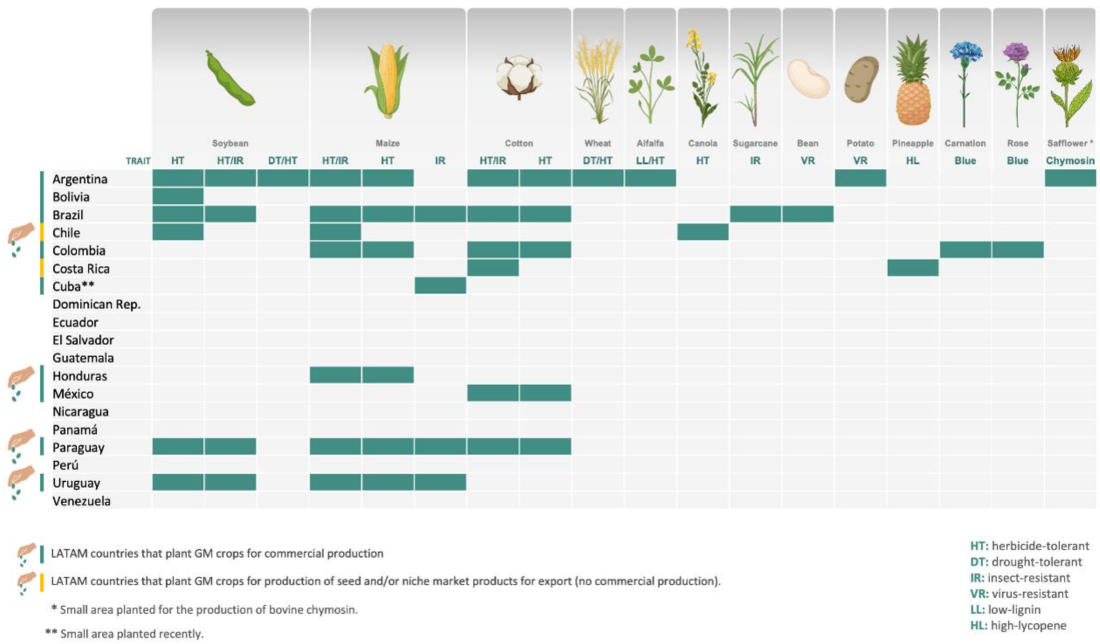
Figure 3



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