

Review

Genetics and Environmental Factors Associated with Resistance to *Fusarium graminearum*, the Causal Agent of Gibberella Ear Rot in Maize

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Abstract: Maize is one of the most important food and feed sources at the worldwide level. Due to this importance, all the pathogens that can infect this crop can harm both food safety and security. Fungi are the most important pathogens in cultivated maize, and *Fusarium* spp. are one of the most important families. Reduction in yield and production of dangerous mycotoxins are the main effects of *Fusarium* spp. infection. *Fusarium graminearum* (part of the *Fusarium graminearum* species complex) is one of the most important fungi that infect maize, and it is the causative agent of Gibberella ear rot (GER). The main characteristics of this species include its ability to infect various species and its varying infection pressures across different years. This fungus produces various harmful mycotoxins, such as deoxynivalenol, zearalenone, butanolide, and culmorin. Infection can start from silk channels or from ear wounds. In the first case, the environmental conditions are the most important factors, but in the second, a key role is played by the feeding action of lepidopteran larvae (in Europe, *Ostrinia nubilalis*). All these factors need to be taken into account to develop a successful management strategy, starting from cropping methods that can reduce the source of inoculum to the direct control of the fungus with fungicide, as well as insect control to reduce ear wounds. But, the most important factor that can reduce the effects of this fungus is the use of resistant hybrids. Different studies have highlighted different defensive methods developed by the plant to reduce fungal infections, like fast drying of silk and kernels, chemical compounds produced by the plant after infection, and mechanical protection from insects' wounds. The aim of this paper is to review the scientific evidence of the most important management strategies against GER in maize and to highlight the genetic basis which is behind hybrid resistance to this disease, with a focus on genes and QTLs found in studies conducted across the world and with different types of maize from tropical cultivars to European flint.

Keywords: maize; *Fusarium graminearum*; GER; corn breeding; review; mycotoxin; DON; ZEA

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1. Introduction

Maize (*Zea mays* L.) is one of the most important cultivated crops. It is the cereal that has seen the highest increase in production rate due to the high demand for maize plant products as important food resources for animals and humans, and as raw materials for use in industry and biofuels [1]. However, cultivation methods (mono-cropping) and poor gene heterogeneity in commercial hybrids have led to a serious problem of disease susceptibility [2,3]. Like all the other crops, maize has a great number of pathogens, among which fungi are some of the most critical [4]. It has been estimated that in the last decade, the average yield loss due to these pathogens ranged from 6.8% to 13.5% [5] in the USA and Canada. Fungal pathogens of maize are relevant not only for the direct damage they can cause to the plant, but also for the ability of many of these pathogens (*Aspergillus* spp.

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and *Fusarium* spp.) to produce mycotoxins [6] (Figure 1). The presence of mycotoxins in corn products (e.g., kernels and silage) can reach almost 100% of the examined samples, due to the large number of possibly toxicogenic fungi that can infect this species [7].

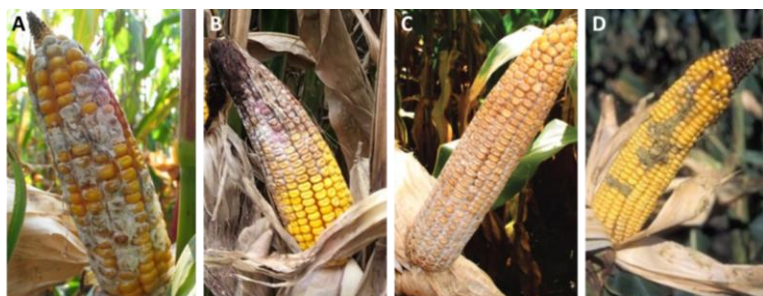


Figure 1. Fusarium ear rot caused by *Fusarium verticillioides*, Gibberella ear rot caused by *Fusarium graminearum*, Diplodia ear rot caused by *Stenocarpella maydis*, and Aspergillum ear rot caused by *Aspergillus flavus*. (A) Fusarium ear rot; (B) Gibberella ear rot; (C) Diplodia ear rot; and (D) Aspergillum ear rot.

Several *Fusarium* species are known to infect maize, and among them, *F. graminearum* Schwabe is one of the most important pathogens. This fungus is sometimes still reported with its teleomorph name of *Gibberella zeae* (Schw.) Petch (Ascomycota). The complex biology of this pathogen has led researchers to define it, rather than as a single species, as the *Fusarium graminearum* species complex (FGSC) [8]. The *Fusarium graminearum* species complex is composed of 16 species: *F. acaciae-mearnsii*, *F. aethiopicum*, *F. asiaticum*, *F. austroamericanum*, *F. boothii*, *F. brasiliicum*, *F. cortaderiae*, *F. gerlachii*, *F. graminearum sensu stricto*, *F. louisianense*, *F. meridionale*, *F. mesoamericanum*, *F. nepalense*, *F. ussuriianum*, *F. vorosii*, and another one that is not yet formally described [9]. The most common species of the FGSC that affects cereals is *F. graminearum*, distributed at a worldwide level. Other important species in cereals are *Fusarium asiaticum*, the most common member of the complex on rice in Asia [10], which is now also present in rice in South America and the USA [11,12]; *Fusarium meridionale*, which is more prevalent in maize in South America; and *Fusarium boothii*, which is the most common species of this complex in South African maize [13]. The reasons for the dominance of one species over the others are not clear, but are correlated to differences in aggressiveness [14] and adaptation to different environments [15]. Other studies consider this fungus not only as part of the *Fusarium graminearum* species complex but also in association with *F. verticillioides* [16]. These two fungi have a complicated interaction, and the presence of one can reduce the effect of the other, but the symptoms in most cases are difficult to distinguish [17] unless the *F. verticillioides*-associated “starburst” is present, leading researchers to study these fungi together. In this review, considering the specific context of breeding resistance traits, *F. graminearum* will be considered as a single species associated with a single disease (Gibberella ear rot), and interaction with other species will be put into the background in order to focus only on the specific effects that this fungus causes in maize.

2. *Fusarium graminearum* (Schw.)

Fusarium graminearum (Ascomycota), also known as *Gibberella zeae* in its sexual stage, is a fungal plant pathogen diffused around the world (Figure 2).

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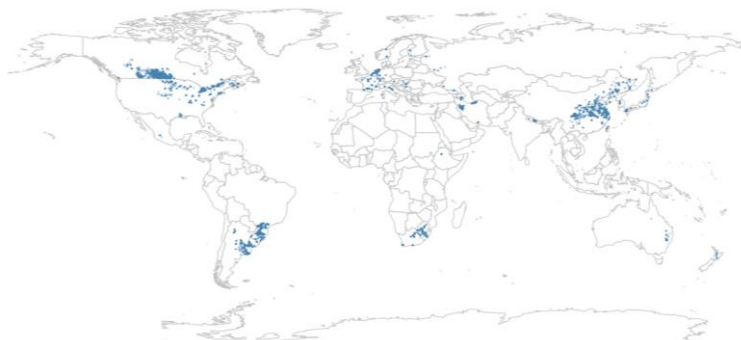


Figure 2. Countries where *Gibberella zeae* has been documented (blue dots). Modified from Del Ponte [8].

Fusarium graminearum is a homothallic and self-fertile fungus. It can have both sexual and asexual life cycles. In its diploid stage, it consists of a fruiting body (perithecium) where ascospores are formed in asci and released in spring [18]. During the haploid phase, it consists of a filamentous hypha and produces mitotic spores (macroconidia). Both ascospores and macroconidia are known as sources of infection [19,20]. It can grow at temperatures between 15 and 29 °C, but when the temperature is higher than 30 °C, its development is very limited [21,22], while on the contrary, some studies have suggested that it can even grow at temperatures below 15 °C [23,24] with a limit of 8 °C for perithecia production [25]. *Fusarium verticillioides*, another pathogen commonly found in cereals, has a higher temperature optimum with a peak development around 27 °C, and it can produce spores even at 45 °C [26]. *F. graminearum* can be found in a large number of cereal grains such as wheat, barley, maize, oats, rice, and rye [27,28]. This fungus can also infect other plant genera like *Pisum*, *Trifolium*, *Solanum*, and *Coffea* [29,30]. It causes a wide range of diseases in various crops, such as head blights in wheat, tuber dry rot in potatoes, and pitch canker of *Pinus* species [29,31–33].

Fusarium graminearum is the causative agent of Gibberella ear rot (GER), which is a key maize disease in temperate regions. It appears as a reddish mold and affects the ear, starting from the tip (Figure 1). Infection can occur starting from the cob or from kernel wounds. When the fungus infects the cob, it appears as a white mycelium, and this turns into a red-pink mold. In severe cases, it can also grow on the husk leaves. In this situation, the husk, cob, and kernels become tightly bound together by the fungal mass, and they are not separable. The infection from the kernel wound has a similar development, but in this case, it seems that the fungus spreads to the top of the ear faster than to the bottom [34]. The amount of yield loss experienced in maize can significantly differ from season to season. According to Sutton's research, there have been years in Canada where serious epidemics of GER (Gibberella ear rot) occurred, while other years saw a much lower impact of this disease [35]. A similar pattern was observed in the United States, as noted by Wetter [36]. In the case of wheat and barley, the culprit behind yield loss is fusarium head blight (FHB) [33,35], a devastating disease that has resulted in losses amounting to tens of billions of dollars over the past two decades in the United States [24,37]. Ascospores are produced from the perithecia outwinter in maize, other cereals' residues, and also a wide range of mono and dicotyledonous weeds (Figure 3) [38–40] when temperatures rise to 13 °C mainly dispersed at night [41].



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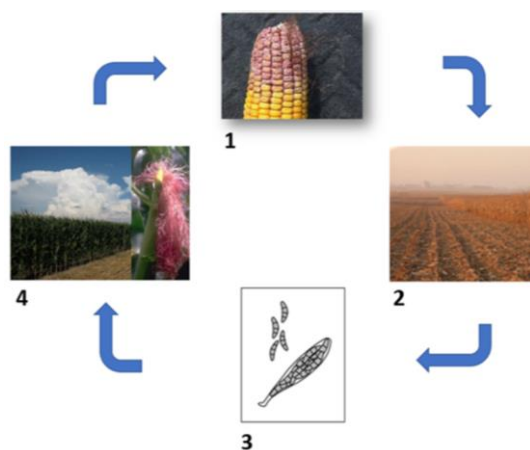


Figure 3. *Gibberella zeae* life cycle. (1) *F. graminearum* appear as a pink or reddish ear mold. (2) Inoculum overwinters in infected crop residues like corn and wheat. (3) *Fusarium graminearum* can grow at temperatures between 15 and 29 °C, and it produces spores starting from 13 °C. (4) Infection occurs at flowering via silk or insect damage.

In corn, infection occurs during the silking period. Ears are more susceptible between two and six days after the emergence of the silk, and the peak of susceptibility is during their senescence [42]. The most common propagation agents of *F. graminearum* are rain, wind, and insects [43,44]. One of the most important insects that are correlated with more severe GER infections is the larva of the European corn borer moth (*Ostrinia nubilalis* Hübner) (Lepidoptera: Crambidae). Tunneling and kernel wounds during the feeding of the larvae can favor the infection by this fungus. The larvae can also spread the propagule with their movements inside the plant [45]. In temperate regions, *O. nubilalis* is normally bivoltine during the maize growing season, but a small number of univoltines or multivoltines can grow depending on the weather [46]. The first-generation larvae usually produce damage to leaves, while the second generation develops by feeding on the stalk or the ears. Tunnels below the ear cause breakage, while apical tunnels in the cob are linked to fungal infection due to a particular microclimatic condition that can promote fungal development [47].

3. Mycotoxins

Reduction in the yield is not the only damage caused by GER: *Fusarium graminearum* is also known to be a mycotoxigenic fungus. Infected maize ears can develop various types of mycotoxins, among which there are some well-established classes, such as aflatoxins, ochratoxins, trichothecenes, fumonisins, and zearalenone, and groups of minor, less-characterized, or emerging toxins for a total of over 30 different mycotoxin types [7,48,49]. The most important are deoxynivalenol and zearalenone, which cause poor livestock performance, particularly in swine. Deoxynivalenol causes feed refusal, vomiting, and decreased weight gain, while zearalenone causes reproductive problems [50,51]. Mycotoxins are secondary metabolites of fungi that have toxic properties to animals and humans [21,52], and they are produced by fungi when these organisms invade crops or their derived products [53,54] (Table 1).

Table 1. Comparison of mycotoxins produced by *F. graminearum* and *F. verticillioides*. Fusarium nomenclature according to Nelson [55].

Fusarium Species	Mycotoxins	Reference
<i>F. graminearum</i>	DON ¹ , ZEN ² , CUL ³ , BUT ⁴	[9,56]
<i>F. verticillioides</i>	FB1 ⁵ , FB2 ⁶ , FB3 ⁷	[57]
<i>F. culmorum</i>	DON, ZEN, NIV ⁸	[58]
<i>F. oxysporum</i>	BEA ⁹	[59]
<i>F. poae</i>	DAS ¹⁰ , NIV, FUS ¹¹	[57]

¹ Deoxynivalenol (Vomitoxin); ² Zearalenone; ³ Culmorin; ⁴ Butenolide; ⁵ Fumonisin B1; ⁶ Fumonisin B2; ⁷ Fumonisin B3; ⁸ Nivalenol; ⁹ Beauvericin; ¹⁰ Diacetoxyscirpenol; and ¹¹ Fusarenone-X (4-Acetyl-NIV).

Due to the risks associated with the intake of mycotoxin-contaminated cereals, different countries and agencies, such as the FAO, FDA, and EFSA, have established regulations to limit their presence in both feed and food. For example, the European Union sets a maximum amount and guidance level for some mycotoxins in grain and derived products [60]. While other fungi of the same genus, such as *Fusarium verticillioides* (Nirenberg), produce mostly fumonisins [57], *F. graminearum* produces various different types of toxins, of which the most important are deoxynivalenol or vomitoxin (DON), zearalenone (ZEN), butanolide (BUT), and culmorin (CUL) [49,56].

4. Deoxynivalenol

Deoxynivalenol (DON) is a mycotoxin of the trichothecene family [61]. DON and its derivatives 3-acetyldeoxynivalenol (3-ADON) and 15-acetyldeoxynivalenol (15-ADON) can be produced on many cereals like corn, wheat, barley, and rice, but also on oats, rye, and sorghum [62]. DON can be produced and accumulates both in the kernels and in the stalk of maize, depending on where the fungus infects the maize plant and, unlike in wheat, it does not seem that the toxin can be transported systemically through different plant organs [63]. *Fusarium graminearum* and *Fusarium culmorum* are the two most important species that produce this toxin. Both species possess strains capable of producing deoxynivalenol (DON) as well as other toxins as their primary metabolites [64]. Both acute and chronic toxicity are associated with DON ingestion. Acute toxicity affects mostly the intestinal mucosa. Overproduction of ROS and reduced respiratory capacities in mitochondria of the host cells and intestinal microbes are the two major causes of this toxicity [65]. The chronic effect is correlated with immune system suppression caused by the inhibition of mitophagy [66]. Other effects of DON are damage to the respiratory system that can lead to asthma [67] and alteration in the expression of MAPK (mitogen-activated protein kinase) proteins that are involved in the control of cell apoptosis, differentiation, and cell growth [68]. Recent studies linked these effects to indirect damage caused by DON to mitochondria, which will ultimately lead to cell death [69].

5. Zearalenone

Zearalenone (ZEN) is a non-steroidal estrogenic mycotoxin [70]. ZEN has a crystalline structure; it is insoluble in water, is heat stable, and has a melting point of 164–165 °C [71,72]. Like DON, *Fusarium graminearum* and *Fusarium culmorum* are the two most important zearalenone fungal producer species [56]. ZEN has been found in all the most important cultivated cereals and some legumes [73–75]. Zearalenone's estrogen-like effects can cause fertility disorders both in humans and animals [76]. At high doses, ZEN induces an overproduction of ROS, thus can lead to oxidative stress. This stress can be correlated with DNA damage and mitochondrial degeneration that can lead to cell apoptosis [77,78]. At lower doses, ZEN is known for its carcinogenic activity in the liver and reproductive system [79].

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6. Butenolide

Butenolide (4-acetamido-4-hydroxy-2-butenic acid lactone or BUT) is a secondary metabolite usually co-produced with other mycotoxins (mostly deoxynivalenol) by different *Fusarium* species, mostly *F. sporotrichioides* and *F. graminearum* [56,80]. BUT is considered an emerging mycotoxin: this classification is used to define all the mycotoxins that are not legislatively regulated but have an important and increasing presence in feed and food [81]. This mycotoxin is associated with the cattle disease known as fescue foot [82,83]: it has been demonstrated to cause damage at the digestive system level due to significant cytotoxic effects caused by oxidative stress and oxidative damage [84,85]. In contrast, its toxicity in the long-term and at lower dosages has not yet been thoroughly studied, and more data are needed [86].

7. Culmorin

Culmorin (CUL) is a tricyclic sesquiterpene diol. Like butanolide and other compounds, it is considered an emerging mycotoxin since it is frequently observed, even in high concentrations, in grain and cereal-based products [86–88]. *F. culmorum* and *F. graminearum* are the two most important CUL producers [56]. A high concentration of this mycotoxin in contaminated grain correlates positively with the DON amount [89]. Taken singly, it seems that this compound does not affect animals or insects [90], but studies demonstrate that it can increase the toxicity of deoxynivalenol. CUL inhibits the glycosylation of DON, which produces less toxic compounds [90,91].

8. Management Strategies to Reduce Infection

Control methods to reduce or mitigate production and quality loss in maize caused by *F. graminearum* can be divided into two broad categories: direct methods that prevent the spread of fungus and infection via the use of synthetic or biological fungicides and/or insecticides, or indirect methods that include the reduction in plant stress or increasing the production of secondary metabolites to prevent the fungal infections via techniques like cropping practices and hybrid selection (Figure 4).

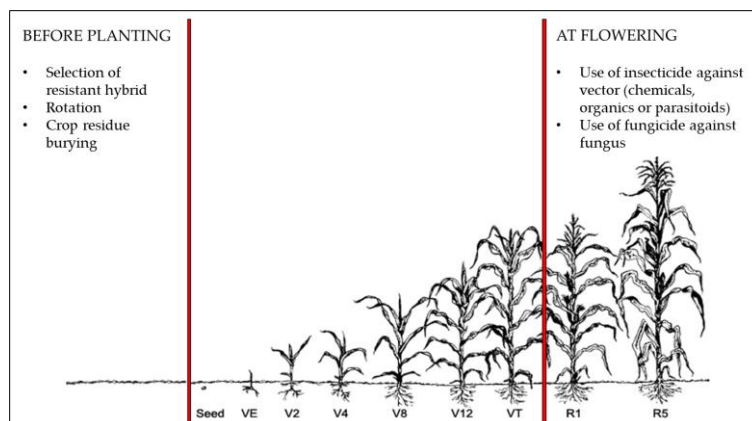


Figure 4. Controls methods in corn cultivation to reduce the impact of Gibberella ear rot (GER). Modified from Lancashire [92].

These control methods may not always be allowed or viable in different areas, as climatic conditions may pose limitations, and different policies in different countries may prohibit or encourage the use of some methods. Fungicide and insecticide applications are

not always available, mostly due to country regulations. Cropping systems that reduce the fungus inoculum, like a crop rotation [44,93], are often not employed, despite the evident advantages that this cropping method can bring [94].

9. Control with Synthetic Fungicides

Worldwide regulations on the use of fungicides on corn can differ a lot, and they can change over the years. While certain countries, such as those in the EU, do not have any registered products specifically designed to control *Gibberella* ear rot, other regions in the world, particularly in South and North America, have witnessed a growing trend in the use of foliar fungicides over the past two decades. Different commercial products are available for *Gibberella* ear rot management in corn [95,96]. The most used active ingredients for the control of GER are prothioconazole and quinone outside inhibitors (QoI). Prothioconazole is a demethylation-inhibiting (DMI) fungicide that interferes with the biosynthesis of ergosterol, a precursor of vitamin D2 and a crucial component of fungal cell walls [97,98]. Quinone outside inhibitors (QoI) are a group of compounds, such as strobilurins, which are active against the protein complex that produces ATP in the fungal cell's membrane, leading to cell death. In particular, QoIs inhibit the transfer of electrons between cytochrome b and cytochrome c1 by the binding of the outer quinol oxidation site (Qo site) [99]. Both groups of fungicides are already used to control *Fusarium* head blight in wheat with different efficacies, where prothioconazole and other triazoles have a better control effect compared to strobilurins [100–103], but in corn, different studies reported that even though these compounds can control symptoms, there are contrasting results for the reduction in mycotoxin levels [102,104,105]. The biggest differences were found in the timing of application of DMI fungicides. The most efficient time of application is at flowering (VT-R2), because most of the available products for this class of fungicide are not fully systemic, and the active ingredient is not able to move from the uptake site to the newly grown tissue [105,106]. Also, DMI fungicides are more efficient in wheat compared to corn, and this could be caused by the husks covering the corn ear, preventing full penetration by the DMI, while the pathogen bypasses this protection by entering via the silks [105]. The availability of only two classes of fungicide may cause the quick development of resistance to these active ingredients in fungal strains placed under strong selective pressure in the field. Studies have already demonstrated the presence of resistance to these fungicides in species like *Cercospora beticola*, *Mycosphaerella graminicola*, *Blumeria graminis*, and others [98,99,106,107].

10. Insecticide against a Vector

The regulations and laws regarding insecticides can vary significantly between countries. However, unlike fungicides used against the pathogen, a range of insecticides are employed to combat Lepidoptera, such as *Ostrinia nubilalis* (Hübner) or *O. furnacalis* (Guenée), which feed on maize. These insecticides primarily belong to the following classes: pyrethroids, organophosphates, carbamates, and anthranilic diamides. Since, as previously stated, fungicide treatments can have a different degree of success regarding the accumulation of mycotoxins, it is often more effective to reduce the damage caused by these fungi by focusing on controlling the insect pests that can facilitate the infection [108]. Pyrethroids are synthetic insecticides derived from pyrethrin, a natural insecticide active against both adults and larvae [47]. Their mode of action is described as preventing the closure of voltage-sensitive sodium channels, causing inactivation of nerves and leading to complete paralysis [109]. Organophosphates inhibit the action of acetylcholinesterase and are also effective against adults and larvae. By preventing the degradation of acetylcholine, a neurotransmitter, these compounds keep synapses in a hyperexcited state, resulting in paralysis [110,111]. Carbamates are another class of compounds that are active against the enzyme acetylcholinesterase, and therefore act in a very similar manner to or-

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ganophosphates [109]. The fourth group of insecticide compounds active against lepidopteran larvae are anthranilic diamides. These compounds cause paralysis of the insect via a different mechanism, affecting the calcium reserves in muscular cells by deregulation of the channels associated with the ryanodine receptor (RyR) [112,113]. The use of an insecticide active against lepidopteran larvae is one of the most important practices to reduce fungal infection and mycotoxin production, especially in countries where fungicides are not available or in a country where GMOs are not permitted [45,114]. For insects, like fungi, resistance to active substances is a reality and is promoted by incorrect insecticide management or uninterrupted usage of insecticides with the same mode of action [115].

11. Biological Control

The use of synthetic fungicides or insecticides is not the only method to control *F. graminearum* infection. According to reports from Reference [116], various approaches that have been successfully utilized and commercially implemented for other crops and against different fungi have been tested for controlling *F. graminearum* infection. They include the use of plant-associated or endophytic micro-organisms, plant growth-promoting bacteria, nontoxicogenic fungal strains, and plant-derived products, which have been tested in recent decades and have proven effective in controlling both symptoms and mycotoxin production. However, no resulting commercial products are yet available on the market at the current date. Another important approach toward successful biological control is targeting *O. nubilalis*. In countries where GMOs that express Cry toxin-related genes from *Bacillus thuringiensis* Berliner (Bt) are permitted, the efficacy of control against ECB and mycotoxin level has proven to be effective [117,118]. In other countries where GMOs are forbidden, there is the possibility of using isolated BT toxins as insecticides [119]. These Cry toxins form pores in the guts of the insects, at first stopping the feeding of the insect and ultimately leading to its death, usually by septicemia. There are different Cry toxins with specificity for different insect groups but, as for other types of insecticides, resistance mechanisms can be developed against this toxin. Resistance in ECB was found to be caused by a mutation in a gut protease, preventing the conversion of the toxin crystalline form into active, monomeric molecules [120]. ECB biological control can also be achieved with the use of parasitoid insects. *Trichogramma* spp. (Hymenoptera), egg parasitoids, are one of the most-used parasitoids to control ECB [121]. In recent decades, different release and distribution methods have been tested, and today, with the introduction of unmanned aerial vehicles in agriculture, the efficacy and feasibility of the use of parasitoid insects have been facilitated [122]. *Trichogramma* spp. is also considered an important factor in the management of BT toxin-resistant insects [123].

12. Cropping Methods

Agronomic practices are fundamental to achieving the highest production in a given environment. They are also one of the most important control methods to reduce the impact of different corn diseases. The most common practices used to control diseases are tillage, crop rotation, optimization of plant density and sowing date, harvest time, and all the agronomic strategies to reduce stress during the whole life cycle of the crop, like irrigation and fertilization. Crop residue management is one of the most important methods to reduce the source of inoculum, since this fungus overwinters in maize stalks and other cereal debris [38,39]. A crop rotation with non-host species is a common strategy for the management of *Fusarium graminearum* in wheat [44,93,124]. In corn, it has been demonstrated that a succession of susceptible species increases the infection rate and the symptoms of this disease [32,125,126]. The positive effects of crop rotations are also related to tillage methods. Conventional tillage associated with plowing is effective in the control of this pathogen in comparison with reduced or no tillage. The burying of crop residues accelerates their decomposition, and the subsequent underground microbial activities are effective in the reduction of inoculum density [32,126]. Of course, the mineralization of

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debris primarily depends on various agronomic conditions and geographical locations worldwide [127]. Planting date is another important factor in the control of different fungal diseases, including GER. Late planting is associated with higher fungal presence; this brings a synchronization of flowering and ECB presence, resulting in greater insect damage and, consequently, higher infection rates [128,129]. Another factor that can affect *F. graminearum* infection is plant density. Higher densities are associated with higher grain contamination. Correct planting density for every cultivated area cannot be easily established because it is affected by the environment, including both persistent and seasonal factors, and different corn genetics that can be more or less suited for a high planting density [130]. In conclusion, different agronomic methods can be applied to reduce the effect of this disease, but the use of resistant hybrids is the most important method to have led to better production in terms of quantity and quality.

13. Hybrid Selection

The use of a resistant variety that does not present symptoms is considered the best practice to reduce GER infection. However, at present, the market can only offer hybrids with a varied range of tolerance, from the ones that present few symptoms to the ones that are severely infected. Even if, during the selection of new maize cultivars, the very susceptible ones are discarded, it's not uncommon to find farmers' fields with infection rates that are above the legal limit in terms of GER-correlated mycotoxins [131]. This is probably due to the fact that GER resistance is a complex quantitative trait, and the actual resistance is influenced by the genotype \times environment interaction [132]. However, several studies have reported both dominant and additive genetic effects correlated with GER resistance [133–135]. Different ear defense mechanisms against fungal infection have been reported. These mechanisms are associated with silk resistance and resistance to the spread of the fungus among the kernels. It is important to note that these two mechanisms are under separate genetic control [136,137]. Kernel resistance is associated with fast drying [138], while silk resistance is associated with faster silk abscission and larger abscission zones [139]. Another type of resistance is associated with the production of defense chemical compounds like maysin and other phenolic compounds associated with antifungal activities. Maysin is a flavone glycoside active in the suppression of insects such as *Helicoverpa zea* (Boddie) and others in maize like *Sitophilus zeamais* (Motschulsky), *Euschistus servus* (Say), and *Nezara viridula* (L.) [140]. The reduction in insect damage is correlated with a reduction in fungal infection [141,142]. Phenolic compounds are produced in corn as a response to fungal infection. It seems that a more resistant variety produces more of this type of compound compared to the susceptible ones. These compounds can also oxidate to produce quinones with an even greater antifungal effect [143,144]. Other important compounds effective against fungal infection are carotenoids. In corn, zeaxanthin has been demonstrated to be effective in the inhibition of DON production due to its effect on the DON biosynthetic pathway [145]. Physical defenses are another type of resistance, and the two major characteristics in maize correlated with the reduction in GER damage are husk tightness and ear attitude. Tight husk germplasm is correlated with a higher GER susceptibility, probably because a favorable microenvironment to fungal proliferation develops inside the ear after heavy rain [146–148]. Another ear characteristic associated with resistance to ear rot is the attitude: a pendant ear attitude is correlated to lower susceptibility to ear rot [131]. To understand the genetic aspects that are behind the phenotypical characteristics associated with GER resistance, various studies have been conducted in recent decades (Table 2).

Table 2. QTLs associated with GER resistance found on different corn materials.

Numbers of Materials	Materials Type	Location	QTL Found	Reference
500	European flint maize landraces	Germany	8	[149]

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244	European dent lines and European flint lines	Germany	8	[150]
204	Chinese recombinant inbred line	China	23	[151]
144	Cross between resistant and susceptible Canadian lines	Canada	29	[136]
759	Cross between resistant Brazilian inbred and susceptible European flint inbred	Germany and Brazil	4	[152]
3	F2 population from resistant and susceptible Chinese inbred	China	17	[153]
298	Population from resistant and susceptible Argentinian inbred	Argentina	4	[154]

A study conducted in Canada that evaluated 144 F2s derived from a cross between one resistant inbred line and a susceptible one found that there was no overlap in the 11 QTLs associated with silk resistance and the 18 QTLs for kernel resistance. Out of the 11 QTLs for silk resistance, 4 were located in chromosome 1, 4 QTLs were on chromosome 7, 2 QTLs were on chromosome 3, and 1 QTL was on chromosome 6. For the QTLs associated with kernel resistance, five QTLs were located on chromosome 7; three QTLs were each on chromosomes 1, 2, and 5; and one QTL was on chromosomes 3, 4, 6, and 9 [136]. In another study of the difference between QTLs associated with GER resistance in the dent and flint materials, similarities in the Manhattan plot for GER resistance and DON accumulation were found, suggesting a possible correlation with fungal resistance and DON concentration [150]. In this study, markers associated with DON resistance for the dent and flint were found in different chromosomes. For the dent materials, the two SNPs were found on chromosomes 2 and 5, and for the flint materials, the six SNPs were located on chromosomes 1, 3, 7, and 9 (Table 3).

Table 3. SNP markers associated with DON resistance [150.]

Marker	Chr.	Bin	Position (bp)	Effect
Dent DON				
SYNGENTA1701	2	2.02	6,474,735	0.26
PZE-105154147	5	5.06	204,425,692	0.4
Flint DON				
SYN11494	1	1.01	3,708,114	0.54
PZE-101242721	1	1.11	289,238,830	0.4
PZE-103000307	3	3.00	1,233,964	0.34
PZE-107039304	7	7.02	75,985,070	0.68
PZE-109079433	9	9.05	127,490,556	0.42
SYN26913	9	9.06	147,467,181	0.45

Other studies with different types of materials like European landraces [149], Chinese inbreds [151,153], Argentinian genotypes [154], and crosses between European and Brazilian inbreds [152] found various QTLs associated with GER resistance in almost all the chromosomes, with considerable difference in the position and number of markers found (Table 4).

Table 4. Position and effect of different SNPs studied in four different studies. pG (%): additive effects and proportion of explained genotypic variance.

Marker/Position	Chr.	Bin	Coordinate (cM)	Range (cM)	Additive Effect	pG (%)	Reference
ZmSYNBREED_24070_673	2	-	49.00	-	5.00	15.04	[149]
ZmSYNBREED_29737_831	2	-	119.54	-	4.56	1.28	

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ZmSYNBREED_30537_486	2	-	162.00	-	-3.33	2.84	
ZmSYNBREED_44869_210	4	-	162.93	-	3.27	4.35	
ZmSYNBREED_47633_944	5	-	78.30	-	3.41	3.27	
ZmSYNBREED_53695_527	6	-	31.15	-	-3.52	6.04	
ZmSYNBREED_55609_889	6	-	91.78	-	-3.14	0.46	
ZmSYNBREED_70955_321	9	-	110.30	-	-4.11	3.53	
qGER1.04	1	1.04	-	122.30–146.21	-0.26	8.85	
qGER2.10	2	2.10	-	270.88–279.05	0.08	1.07	
qGER3.02	3	3.02	-	41.8–70.39	-0.31	7.75	
qGER3.06	3	3.06	-	208.96–223.41	0.13	4.92	
qGER4.05	4	4.05	-	101.37–133.51	0.11	5.24	
qGER4.09	4	4.09	-	251.87–286.56	-0.47	9.05	[151]
qGER7.03	7	7.03	-	162.71–170.86	0.18	3.86	
qGER8.05	8	8.05	-	172.23–194.04	-0.15	6.9	
qGER9.06	9	9.06	-	124.87–146.66	-0.24	4.01	
qGER10.06	10	10.06	-	139.61–149.5	0.04	1.98	
qGER10.07	10	10.07	-	198.11–211.71	0.03	3.08	
T3 x A6_A7 q1	1	1.02	60.54	58.89–62.92	-0.96	10.17	
T3 x A6_A7 q2	3	3.08	196.72	194.99–197.03	-1.33	14.86	
T3 x A6_A7 q3	5	5.06	162.53	161.56–162.71	-0.43	5.37	
T4 x A4_A5 q1	1	1.02	58.64	50.40–85.62	0.35	10.92	[152]
T4 x A4_A5 q4	8	8.05	120.04	119.75–120.56	0.35	11.67	
T3 x A8 q1	1	1.02	60	59.93–61.04	-0.34	21.84	
qRger7.1	7	7.02	-	121.10–151.20	0.62	20.16	
qRger10.1	10	10.01–10.03	-	22.80–60.70	-0.42	10.18	
qRger2.1	2	2.01–2.02	-	6.10–33.70	0.36	7.27	
qRger2.2	2	2.02–2.03	-	33.70–75.80	-0.11	23.79	
qRger4.1	4	4.01–4.02	-	0.00–28.20	0.43	8.55	
qRger6.2	6	6.05–6.06	-	74.00–109.50	-0.65	10.47	
qRger7.2	7	7.01–7.02	-	35.60–62.00	0.43	14.09	
qRger9.1	9	9.01	-	6.00–29.30	0.38	5.97	
qRger1.1	1	1.03	-	52.60–76.10	0.63	15.09	[153]
qRger2.3	2	2.04–2.07	-	87.90–116.80	0.58	9.97	
qRger3.1	3	3.08–3.09	-	170.70–196.80	-0.41	7.25	
qRger4.2	4	4.04–4.05	-	64.00–88.00	0.76	13.55	
qRger4.3	4	4.05–4.07	-	83.20–108.80	0.53	12.03	
qRger5.1	5	5.04–5.05	-	93.00–123.3	0.6	10.62	
qRger6.1	6	6.00–6.01	-	2.90–26.10	-0.51	8.4	
qRger7.3	7	7.03–7.04	-	131.80–161.00	0.4	4.81	
qRger9.2	9	9.02–9.05	-	70.00–94.20	-0.51	10.37	

This can only confirm the nature of quantitative traits of GER resistance. Despite the challenges faced, a study aimed at identifying genes linked to this resistance was carried out, leading to the discovery of four genes located on chromosome 2 that showed a correlation with kernel resistance [155].

14. Conclusions

Interactions between *Fusarium graminearum* and corn are complex, and a great number of factors can contribute to the development of infection or resistance of the corn plant. Differences between cropping seasons seem to have a great impact on the damage caused by this disease [35,36]. Cropping methods are another important factor, but in this case,

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useful actions to control GER can be difficult to implement, due to economic sustainability, like a rotation, or on the contrary, environmentally sustainable methods like no tillage can increase the impact of this disease [32,93]. In the end, the use of insecticides to control the vector or fungicide to directly control the fungus may not be economically convenient and can cause the development of resistant populations [106,107,115]. The use of genetically modified organisms can be useful to control the vector, but they are not available everywhere [117,118]. Biological methods to control this fungus are still in development, and no commercial products are available [116].

In conclusion, the selection of resistant hybrids is one of the most important and viable control methods. Hybrids with greater resistance will permit a reduction in the use of pesticides and, therefore, make the development of resistant pests less likely (both fungi and insects). The use of modern breeding technologies like genome prediction and marker-assisted selection can improve the development of more resistant materials in the framework of more sustainable agriculture.

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Data Availability Statement:

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Commentato [M65]: We added the page number. Please confirm. The following highlights are the same.

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