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Effects of β-estradiol on the Phytopathogenic Fungus *Fusarium graminearum*

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Estrogen, a key sex hormone in humans and other mammals, regulates the female reproductive system and has important medicinal applications. It enters the environment through sources such as animal feces and medical waste. It is structurally similar to the mycotoxin zearalenone produced by the homothallic fungus *Fusarium graminearum*. This fungus is responsible for causing Fusarium head blight on cereal crops around the world. We investigated the effects of the major estrogen, β-estradiol, on the development of *F. graminearum*. β-estradiol increased the production of asexual conidia and sexual perithecia in this fungus. It also accelerated conidial germination of *F. graminearum*, *Fusarium solani*, and *Fusarium oxysporum*. Furthermore, it restored mycelial growth under membrane stress and enhanced survival under oxidative and cold stress conditions. It also affected mycotoxin production. These findings suggest that estrogen pollution would influence the life cycle of *F. graminearum* and the interactions between plant pathogens and plants.

Keywords **:** β-estradiol, estrogen, *Fusarium graminearum*, Fusarium head blight, zearalenone

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Estrogen is a hormone primarily associated with the female reproductive system, responsible for the development of female sexual characteristics and playing roles in the skin, skeletal, and cardiovascular systems (Huether and McCance, 2019). Synthetic estrogens are also widely used in contraception and hormone replacement therapy. Estrogens enter the environment through agricultural runoff, where livestock feces are used as fertilizer, as well as through dairy wastewater, domestic sewage, and medical waste (Rechsteiner et al., 2020; Yang et al., 2021). Environmental estrogens negatively affect animal health, causing reproductive organ abnormalities, disruptions in cell death processes, and even cancer (Wojnarowski et al., 2021). Research into the impact of estrogen on plants has gained momentum since the 2000s, revealing its influence on plant growth, reproduction, metabolism, stress response, and pathogen resistance (Janeczko, 2021).

Certain fungi also respond to mammalian sex hormones. For instance, increased host estrogen levels are associated with a higher risk of vulvovaginal candidiasis, as observed in cases of pregnancy, oral contraceptive use, and hormone replacement therapy. Estrogen has been shown to enhance the virulence of *Candida albicans* by promoting its germination and allowing it to evade the innate immune system (Cheng et al., 2006; Kumwenda et al., 2021). Moreover, *C. albicans* has an estrogen-binding protein that binds to mammalian estrogens (Madani et al., 1994). Another ex-

ample is Paracoccidioidomycosis, a fungal disease caused by *Paracoccidioides brasiliensis*, which is more prevalent in men than women, suggesting a protective role of estrogen in women. In this fungus, estrogen inhibits or delays the transition from mycelium to yeast at the infection site (Restrepo et al., 1984), possibly through receptor-like cytosol binding proteins (Loose et al., 1983). Similarly, estrogen regulates the cell cycle in *Saccharomyces cerevisiae*, which also possesses estrogen-binding proteins (Burshell et al., 1984; Tanaka et al., 1989). Fascinatingly, this yeast produces a substance with estrogenic activity in mammalian systems (Feldman et al., 1984) and even synthesizes estradiol under specific culture conditions (Miller et al., 1986). However, despite the significant environmental impact of estrogen, no research has yet explored its effects on phytopathogenic fungi.

The ascomycete fungus *Fusarium graminearum* is a major phytopathogen responsible for Fusarium head blight in small grains and ear rot in maize. This fungus also produces zearalenone (ZEA), an estrogenic mycotoxin that disrupts hormonal balance in humans and animals (McMullen et al., 2012). ZEA, with its structural resemblance to β-estradiol, binds to estrogen receptors and causes reproductive issues such as infertility and miscarriage in mammals (Kowalska et al., 2016). *F. graminearum* produces both sexual spores (ascospores) in perithecia and asexual spores (conidia). Primary infections begin with ascospores, while secondary infections spread through vegetative growth and conidia, particularly under stress conditions. These infections not only cause significant yield and quality losses but also contaminate crops with harmful mycotoxins like deoxynivalenol (DON) and ZEA. DON acts as a virulence factor, causing tissue necrosis and allowing the fungus to spread within plants (Trail, 2009).

Although ZEA's role in regulating sexual reproduction has been suggested, its exact function remains unclear due to limited evidence (Wolf and Mirocha, 1977). A previous study found that among various animal and plant estrogens, β-estradiol regulates the ZEA-inducible promoter at a level comparable to ZEA (Lee et al., 2011a, 2011b). Consequently, we focused on β-estradiol to examine its effects on the life cycle and survival of *F. graminearum*. Our research highlighted the potential impact of environmental estrogen contamination on the phytopathogenic fungus *F. graminearum*.

Materials and Methods

Fungal strains and culture conditions. The wild-type *F. graminearum* strains GZ03639 (Bowden and Leslie, 1999) and PH-1 were cultivated according to the *Fusarium* laboratory manual (Leslie and Summerell, 2006). Strains were maintained on potato dextrose agar (PDA), and radial growth was measured on minimal media (MM) at 25°C. Conidia production was induced in carboxymethyl cellulose (CMC) (Capellini and Peterson, 1965) and on yeast malt agar (Harris, 2005). Sexual reproduction was induced using carrot agar (CA) as previously described (Lee et al., 2008).

Mycelial growth and conidial production. The effect of β-estradiol on vegetative growth was assessed by inoculating GZ03639 and PH-1 strains onto MM supplemented with 0, 5, or 50 μg/ml β-estradiol. Water-soluble β-estradiol (E4389, Sigma-Aldrich, St. Louis, MO, USA) was dissolved in distilled water for use. Strains were cultivated at 25°C for 3 days, after which mycelial growth was evaluated. To evaluate the effect of β-estradiol on conidia production, three equally sized mycelial plugs were inoculated into CMC containing 0, 5, or 50 μg/ml β-estradiol and incubated at 25°C with shaking at 200 rpm for 5 days. Cultures were filtered through two layers of Miracloth, and conidia were harvested by centrifugation at 13,000 rpm. The total number of conidia was then counted using a hemocytometer.

Conidial germination. Harvested conidia as described above were washed twice with distilled water and resuspended in MM liquid. To assess the impact of β-estradiol on conidial germination, conidia of each fungal strain were incubated at a final concentration of 10^6 conidia/ml in MM liquid containing 0, 5, or 50 μg/ml of β-estradiol. Conidial germination was observed and quantified at 4 and 8 h using light microscopy.

Stress tests. Stress tests were conducted on mycelia and conidia following the methods described by Zheng et al. (2012) with slight modifications. For the cell membrane stress test, mycelial plugs were inoculated onto MM supplemented with 0, 5, or 50 μg/ml β-estradiol and 0, 0.01, or 0.02% sodium dodecyl sulfate (SDS) and incubated at 25°C for 3 days. For the cell wall stress test, mycelial plugs were inoculated onto MM supplemented with 0, 5, or 50 μg/ml β-estradiol and 0 or 60 μg/ml Congo red. In the oxidative stress test, mycelial plugs were incubated on MM supplemented with 0, 5, or 50 μg/ml β-estradiol, as well as 0 or 5 mM H_2O_2, or 100 and 150 μM menadione, and incubated at 25°C for 3 days. Colony diameters were measured for all tests.

Stress tests were also performed on conidia. Conidial

suspensions (10^6 conidia/ml) were cultured in MM liquid supplemented with 0, 5, or 50 μg/ml β-estradiol and 100-125 μM menadione. Cultures were incubated at 25°C with shaking at 200 rpm, and the number of germinated spores was counted after 3 days. For cold stress tests, conidial suspensions (10^3 conidia/ml) were incubated in MM liquid containing 0, 5, or 50 μg/ml β-estradiol and stored at 4°C for 1-3 days. Subsequently, 100 μl of each suspension was spread onto PDA, and the number of germinated spores was counted after 2 days (Li et al., 2019).

Fertility test. The self-fertilization test was conducted following the method of Lee et al. (2008). Mycelia were grown on CA with 0, 5, or 50 μg/ml β-estradiol at 25°C in the dark for 4 days. After this period, the mycelia were removed using a surgical blade, and 1 ml of a 2.5% Tween-60 solution was applied. All cultures were incubated under near-ultraviolet light (20 W, 500 lux) at 25°C for 8 days. The number of perithecia was counted by photographing five regions per plate using a microscope, with three replicates per experiment. A perithecium was considered mature if its diameter was at least 120 μm, based on previous findings (Lee et al., 2008). Forcible ascospore discharge was observed in small acrylic chambers, as described by Son et al. (2013). A semi-circular agar block (10 mm in diameter), covered with 8-day-old perithecia, was placed on a coverslip and incubated in the chamber for 3 days.

Mycotoxin production. To analyze DON and 15-acetyldeoxynivalenol production, conidial suspensions (10^4 conidia/ml) of each strain were inoculated into agmatine minimal medium supplemented with 0, 5, or 50 μg/ml β-estradiol. Cultures were incubated under stationary conditions at 25°C for 7 days. Trichothecenes were extracted by mixing 150 μl of culture filtrate with 250 μl of an ethyl acetate-methanol solution (4:1, v/v). The extracts were dried using nitrogen, then dissolved in 100 μl of distilled water. DON levels were quantified using DON enzyme-linked immunosorbent assay (ELISA) kit (CUSABIO, College Park, MD, USA) according to the manufacturer's protocol (Oh et al., 2016).

The extraction and analysis of ZEA were carried out as described by Lee et al. (2011b). Conidial suspensions (10^3 conidia/ml) from each strain were cultured in CM liquid medium at 25°C with shaking at 200 rpm for 3 days. The filtered mycelia were then transferred to starch glutamate medium supplemented with 0, 5, or 50 μg/ml of β-estradiol, and incubated at 25°C under stationary conditions for 7 days. In brief, 10 ml of the culture filtrate was defatted with 10 ml of n-hexane and extracted twice using 10 ml of ethyl acetate. The ethyl acetate layer was then concentrated to dryness and reconstituted in 1 ml of methanol. ZEA levels in each strain were quantified using a Zearalenone ELISA kit (Demeditec Diagnostics GmbH, Kiel, Germany) according to the manufacturer's instructions.

RNA-seq analysis. Conidial suspensions (10^4 conidia/ml) of each strain were inoculated in MM liquid containing 0, 5, or 50 μg/ml β-estradiol and incubated at 25°C with shaking at 200 rpm for 8 h. Total RNA was extracted using the easy-spin Total RNA Extraction Kit (iNtRON Biotechnology, Seongnam, Korea) in accordance with the manufacturer's instructions. Whole transcriptomes of each strain were sequenced using the Illumina NovaSeq platform at Macrogen (Seoul, Korea).

Results

Effects of β-estradiol on mycelial growth and conidial production. No significant differences in vegetative growth were observed in strains treated with β-estradiol and those without treatment. However, conidial production significantly increased in response to β-estradiol treatment. Compared to the control, GZ03639 exhibited a six-fold increase when treated with 5 μg/ml β-estradiol and more than a 20-fold increase with 50 μg/ml β-estradiol. PH-1 showed a two-fold increase at 5 μg/ml β-estradiol and over a 12-fold increase at 50 μg/ml β-estradiol (Fig. 1).

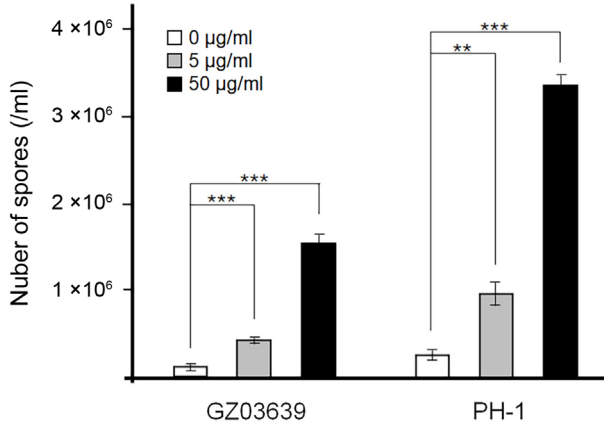

Fig. 1. Effect of β-estradiol on conidial production. Each strain was inoculated into carboxymethyl cellulose supplemented with either 5 or 50 μg/ml β-estradiol, and the cultures were shaken 200 rpm at 25°C. After 5 days, conidial production was assessed using a hemocytometer. Asterisks indicate statistical significance (**$P \leq 0.01$, ***$P \leq 0.001$) based on *t*-test comparisons. Data are presented as mean ± standard deviation.

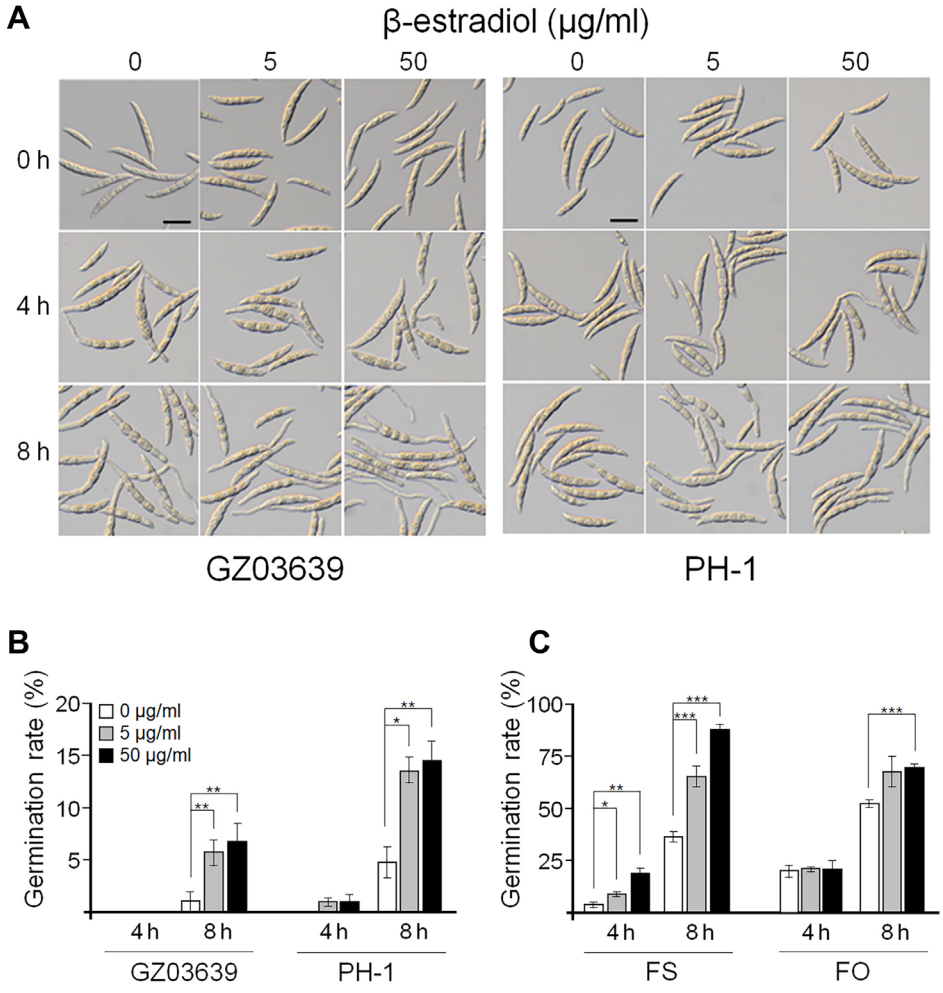

Fig. 2. Effect of β-estradiol on conidial germination. (A, B) Conidia of GZ03639 and PH-1 strain were inoculated into minimal media liquid, and the cultures were shaken at 200 rpm at 25°C. Conidia germination was observed at 4 and 8 h post-incubation using an optical microscope. Scale bar = 20 μm. (C) Conidial germination of *Fusarium solani* (FS) and *F. oxysporum* (FO) was observed at 4 and 8 h after incubation. Asterisks indicate significant differences (*$P \leq 0.05$, **$P \leq 0.01$, ***$P \leq 0.001$) based on *t*-test comparisons. Data are presented as mean ± standard deviation.

Effect of β-estradiol on conidial germination. Conidial germination of all strains tested was enhanced by β-estradiol. Germination was considered to have occurred when the germ tube exceeded the length of the conidium. After 8 h, the conidial germination rates for GZ03639 and PH-1 strains increased by more than two-fold when treated with β-estradiol compared to the control. Additionally, conidial germination rates for *Fusarium solani* and *Fusarium oxysporum* increased after 4 and 8 h of β-estradiol treatment (Fig. 2).

Effect of β-estradiol on stresses. Mycelial growth recovered to a notable degree when strains were treated with β-estradiol in combination with the cell membrane inhibitor SDS, particularly at a concentration of 50 μg/ml (Fig. 3). In the cell wall stress test, while vegetative growth length showed no significant change, abundant aerial hyphae and improved mycelial growth were observed in β-estradiol-treated samples (Fig. 3). Additionally, β-estradiol treatment reduced sensitivity to intracellular oxidative stress induced by menadione (Fig. 4). Although no major changes were observed in vegetative growth length under extracellular oxidative stress (H_2O_2), enhanced aerial hyphae and visible mycelial recovery were evident in the β-estradiol-treated strains (Fig. 4).

The β-estradiol treatment also reduced sensitivity to oxidative and cold stresses in conidia. In the oxidative stress test, conidial germination rate of GZ03639 decreased after treatment with 125 μM menadione, regardless of β-estradiol presence. However, the germination rate fully

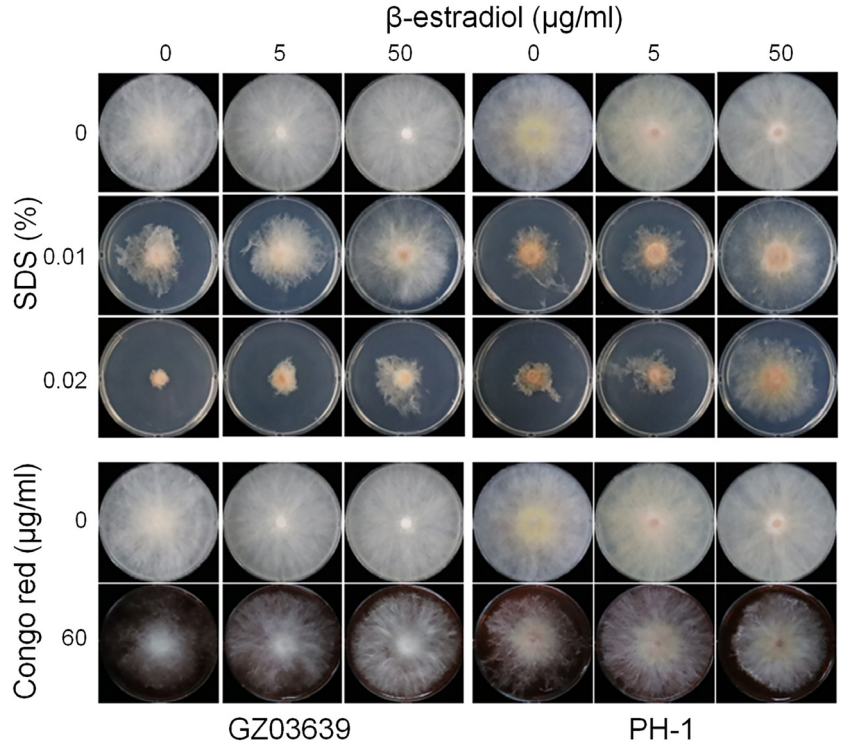

Fig. 3. Effect of β-estradiol on stresses related to cell membrane (SDS) and cell wall (Congo red). Each strain was grown on minimal media supplemented with either SDS (0.01 or 0.02%) or Congo red (60 μg/ml), along with 5 or 50 μg/ml β-estradiol and incubated at 25°C for 3 days.

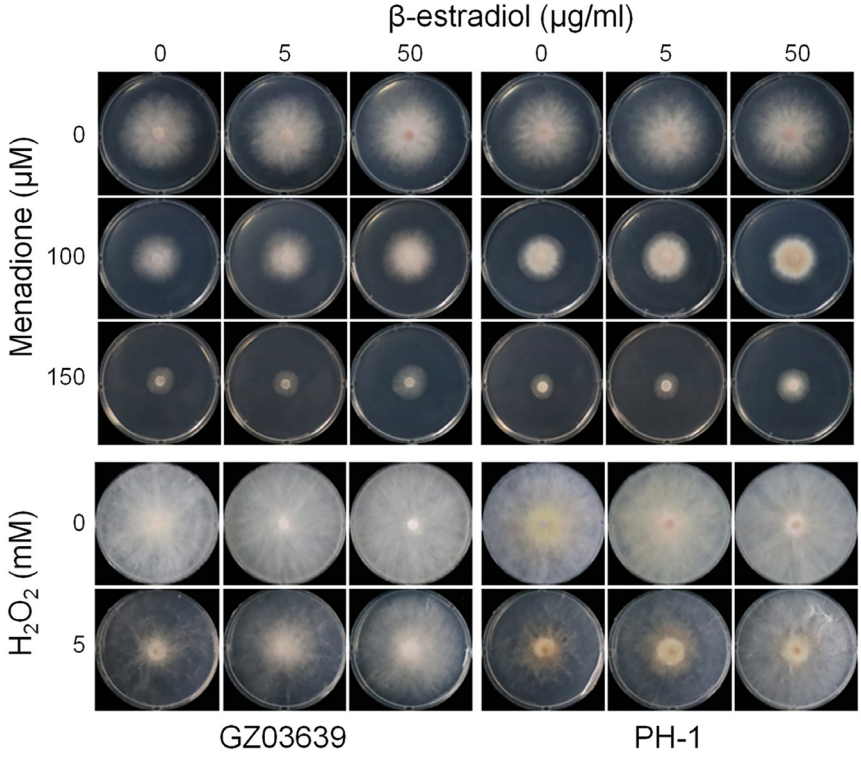

Fig. 4. Effect of β-estradiol on intracellular (menadione) and extracellular (H_2O_2) oxidative stresses. Each strain was grown on minimal media supplemented with either menadione (100 or 150 μM) or H_2O_2 (5 mM), along with 5 or 50 μg/ml β-estradiol and incubated at 25°C for 3 days.

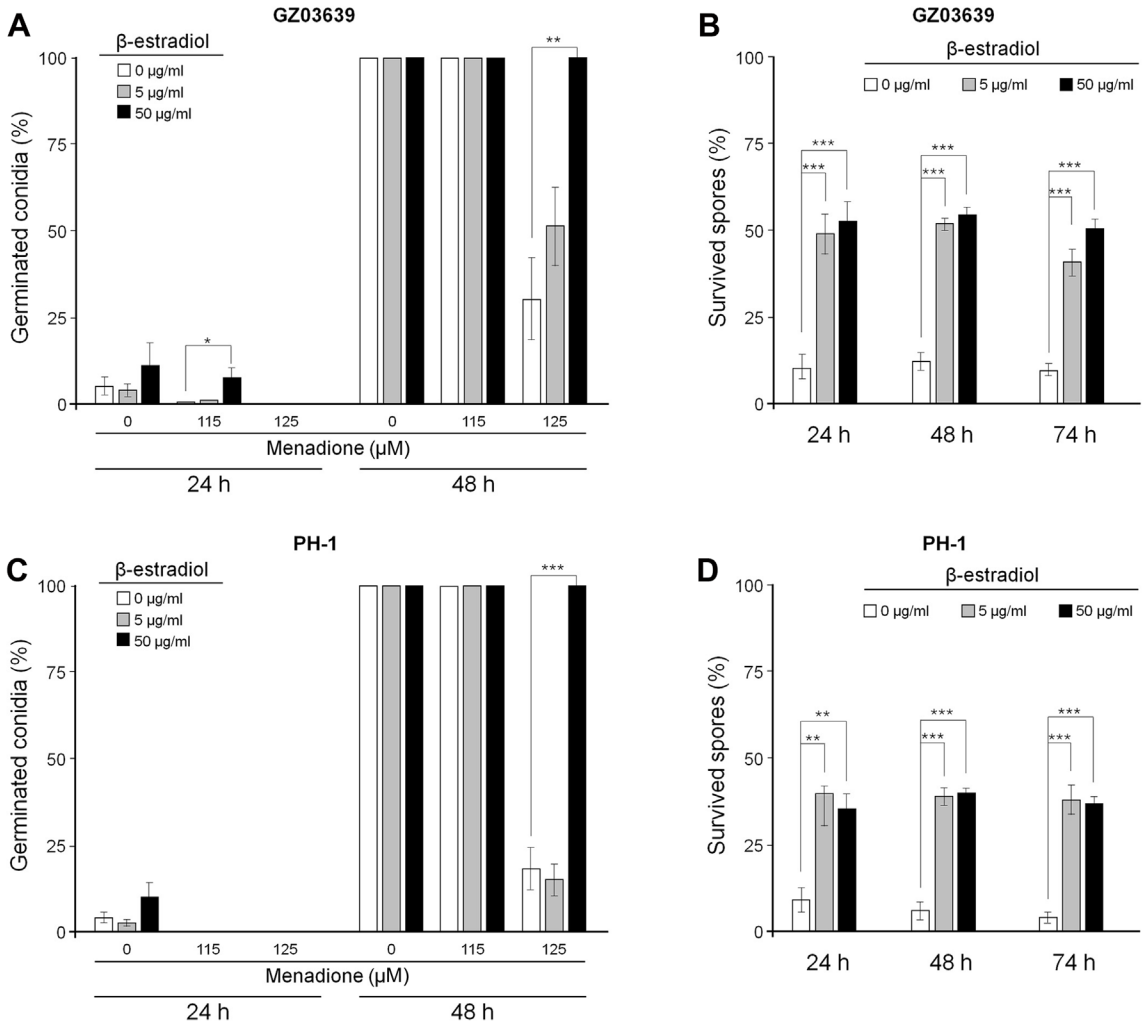

Fig. 5. Effect of β-estradiol on conidial resistance to oxidative and cold stress. (A, C) Conidial suspensions were cultured in minimal media (MM) supplemented with 5 or 50 μg/ml β-estradiol and 115 or 125 μM menadione, then incubated at 25°C with shaking at 200 rpm for 2 days. (B, D) Conidial suspensions were incubated in MM containing 5 or 50 μg/ml β-estradiol and stored at 4°C for 1-3 days. Subsequently, 100 μl of each suspension was spread onto potato dextrose agar, and the number of surviving conidia was counted after 2 days. Asterisks indicate significant differences (*$P \leq 0.5$, **$P \leq 0.01$, ***$P \leq 0.001$) based on *t*-test comparisons. Data are presented as mean ± standard deviation.

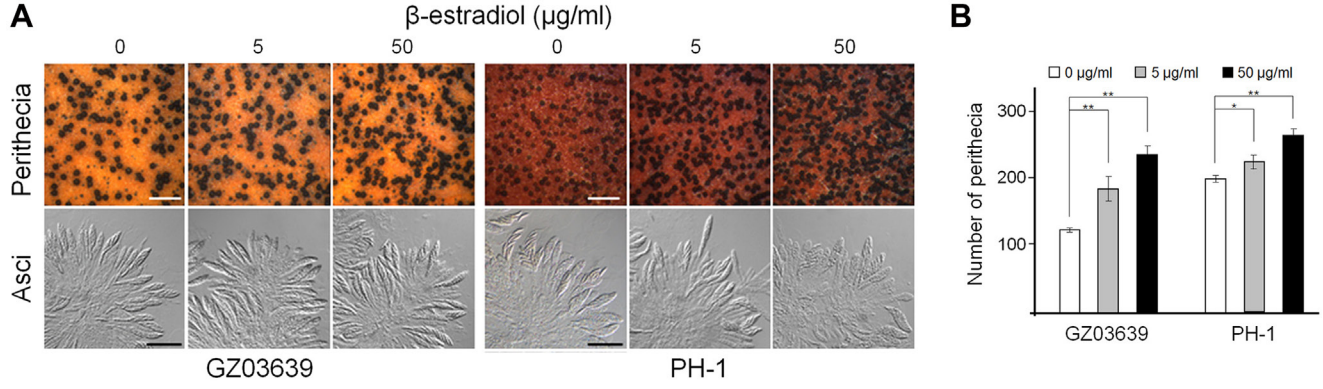

Fig. 6. Effect of β-estradiol on sexual development. (A) Perithecia and asci produced on carrot agar (CA) (white scale bars = 1 mm, black scale bars = 50 μm). (B) The number of perithecia produced on CA. Asterisks indicate significant differences (*$P \leq 0.05$, **$P \leq 0.01$) based on *t*-test comparisons. Data are presented as mean ± standard deviation.

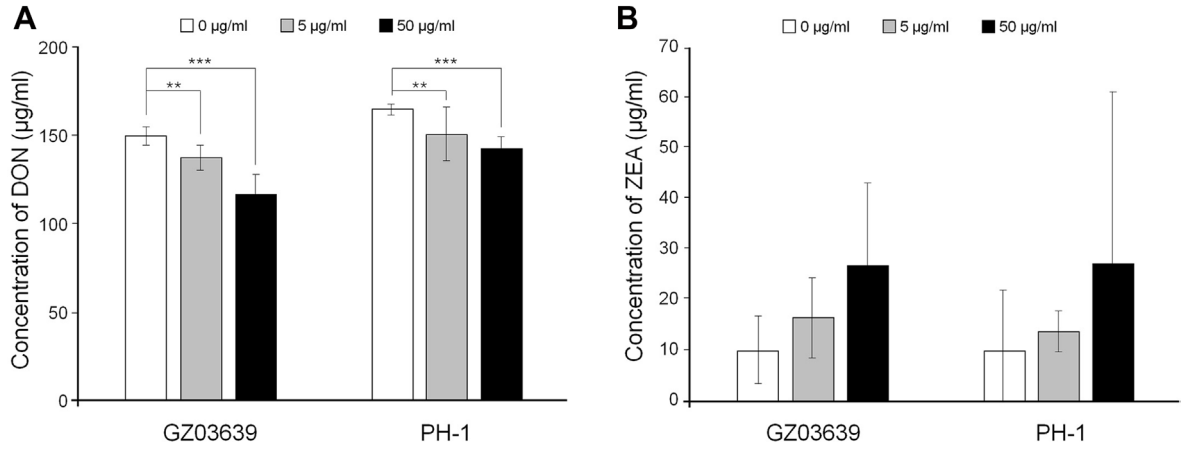

Fig. 7. Effect of β-estradiol on mycotoxins, deoxynivalenol (DON) (A) and zearalenone (ZEA) (B) production. Asterisks indicate significant differences (**$P \leq 0.01$, ***$P \leq 0.001$) based on *t*-test comparisons. Data are presented as mean ± standard deviation.

recovered in the group supplemented with both 125 μM menadione and 50 μg/ml β-estradiol after 2 days (Fig. 5A). When treated with 115 μM menadione for PH-1, the germination rate decreased on day 1 but fully recovered 2 days later in the group supplemented with 115 μM menadione and 50 μg/ml β-estradiol (Fig. 5C). In the cold stress test, both strains showed significantly higher survival rates at low temperatures when β-estradiol was added, compared to the groups without β-estradiol (Fig. 5B and D).

Effect of β-estradiol on sexual development and mycotoxin production. The number of perithecia produced increased by β-estradiol but ascospore maturation was not affected (Fig. 6). Additionally no difference was observed in ascospore discharge between the control and treatment groups (data not shown).

DON production decreased across all β-estradiol treatments (Fig. 7A). ZEA production showed a tendency to increase with β-estradiol treatment, but this change was also not statistically significant (Fig. 7B).

Transcriptome analyses upon β-estradiol treatment. RNA-seq analyses were conducted to profile the gene expression patterns of the GZ03639 strain in response to

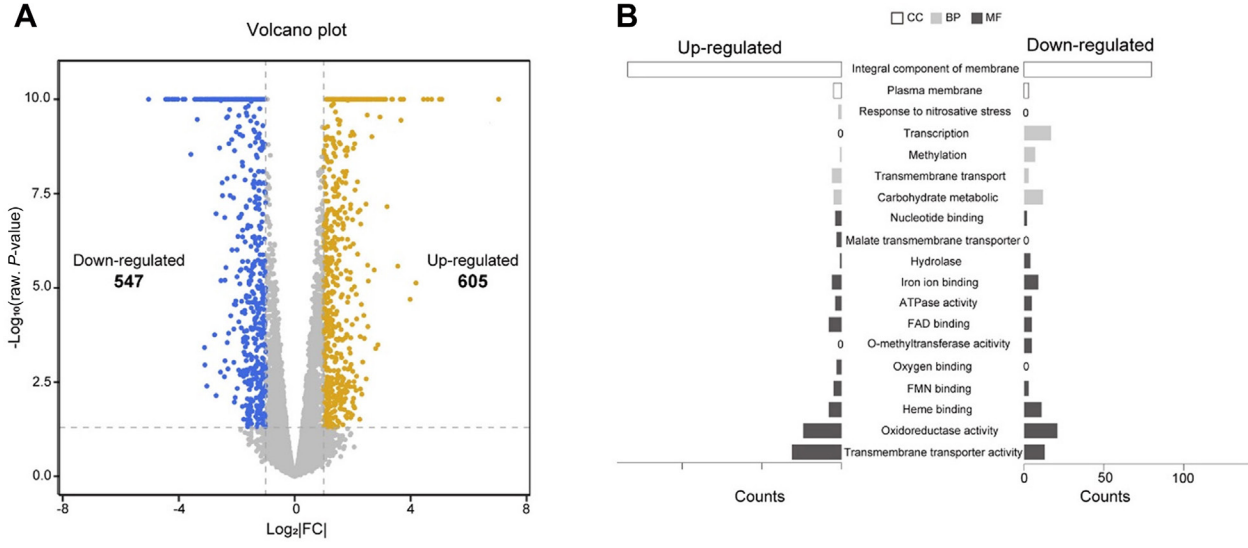

Fig. 8. Transcriptome analyses upon β-estradiol treatment. (A) Distribution of transcripts shown as a Volcano plot. Differentially expressed genes (DEGs) with a cutoff of $P < 0.05$ are displayed, with vertical lines indicating the thresholds of $|\text{Log}_2 \text{FC}| \geq 2$. (B) Top enriched gene ontology (GO) terms of DEGs. Top enriched GO terms of the DEGs are ranked by the number of genes. BP, biological process; CC, cellular component; MF, molecular function.

β-estradiol. The transcriptome data have been deposited in the Sequence Read Archive at the National Center for Biotechnology Information under the accession number PRJNA1185832. Using a threshold of a two-fold or greater change in expression, 605 genes were found to be upregulated, while 547 genes were downregulated following β-estradiol treatment (Fig. 8A). To classify the functions of the differentially expressed genes, gene ontology (GO) analysis was performed, focusing on the top GO classification in cellular component, biological process, and molecular function categories (Fig. 8B). The GO analysis revealed that the upregulated transcripts were predominantly associated with terms such as integral component of membrane, plasma membrane, response to nitrosative stress, transmembrane transport, nucleotide binding, malate transmembrane transporter, FAD binding, oxygen binding, oxidoreductase activity, and transmembrane transporter activity. Conversely, the downregulated transcripts were primarily linked to transcription, methylation, carbohydrate metabolic process, hydrolase activity, iron ion binding, ATPase activity, O-methyltransferase activity, and heme binding.

Discussion

This study originated from the discovery that β-estradiol, among various mammalian estrogens, can regulate the ZEA-inducible promoter at the level of ZEA, making it a viable substitute for ZEA in experimental systems involving the *Fusarium* genus (Lee et al., 2011a). Using β-estradiol, we examined its effects on the species level of *F. graminearum*, focusing on the GZ03639 and PH-1 strains, which are widely used wild-type strains in research globally. *F. graminearum* infects plants through either asexual conidia or sexually derived ascospores. Of these, the ability of conidia to attach to host tissue and germinate likely plays a key role in the localized spread of Fusarium head blight. In this study, we found that β-estradiol enhanced conidial germination in *F. graminearum*, *F. solani*, and *F. oxysporum* (Fig. 2C). Thus, we anticipate that mammalian estrogens may significantly influence the initial infection and colonization of plants by phytopathogenic fungi.

When the fungi were exposed to various abiotic stresses, β-estradiol treatment showed a tendency to restore mycelial growth. This effect was particularly pronounced when treated with SDS, which affects cell membrane integrity. RNA-seq analysis revealed increased expression of genes essential for membrane structure, along with differences in the expression of genes involved in transmembrane transport (Fig. 8B). These findings suggest that β-estradiol plays a role in material transport and signal transduction in the fungus.

Fungal conidia are produced to ensure fungal survival under nutrient-deprived conditions or harsh environments and play a crucial role in dispersal, allowing the fungus to exploit new niches, including susceptible plant tissues (Seong et al., 2008). During dispersal, conidia float in the air, uncertain of when they will encounter a new host, and face a high risk such as various abiotic stresses. In this study, β-estradiol treatment was found to increase conidia production and improve conidial survival under stresses such as oxidative and cold stress (Fig. 5). Therefore, environmental estrogens may enhance fungal conidia production and dispersal, while also improving their survival during the process.

The fungus overwinters as perithecia in soil or crop residues, which serve as a source of primary inoculum in the spring. Ascospores produced and released from these perithecia play a crucial role in spreading the disease during the flowering season. In this study, perithecia production increased by β-estradiol. Since perithecia are survival structures formed under harsh conditions, these findings suggest that β-estradiol enhances the survival of this fungus during winter.

Among the trichothecenes, DON plays a crucial role in the spread of Fusarium head blight within a wheat spike (Bai et al., 2002). Our study showed that β-estradiol decreased DON production (Fig. 7A). DON production is regulated by external stresses such as oxidative, temperature, and biotic factors that act as environmental triggers (Audenaert et al., 2010). Thus, the decrease in DON production observed here is likely due to β-estradiol enhancing the fungus's resistance to various stresses.

Previous studies on the effects of estrogen on fungi have primarily focused on the vegetative and asexual reproduction stages. However, fungi have a much more complex and diverse life cycle in nature. In this study, we demonstrated that estrogen influences not only vegetative and asexual reproduction but also mycotoxin production, and resistance to abiotic stresses. These findings provide evidence that estrogen can significantly impact the life or disease cycle of *F. graminearum*. This study also highlights the environmental concerns surrounding estrogen pollution and offers an evolutionary perspective on the potential role of ZEA in *F. graminearum*.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

Acknowledgments

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