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Flubendiamide provokes oxidative stress, inflammation, miRNAs alteration, and cell cycle deregulation in human prostate epithelial cells: The attenuation impact of synthesized nano-selenium using *Trichoderma aureoviride*

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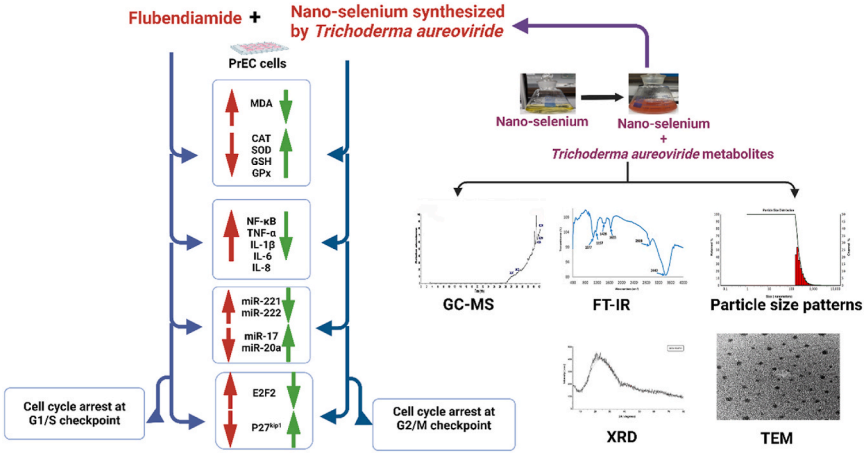
HIGHLIGHTS

- FBD promoted oxidative stress and pro-inflammatory response.
- FBD caused upregulation of miR-221/222 and downregulation of miR-17/20a.
- FBD altered the protein level of E2F2 and $P27^{kip1}$.
- FBD caused cell cycle arrest at the G_1/S checkpoint and apoptosis.
- T-SeNPs rescued the insecticide's adverse effects.

GRAPHICAL ABSTRACT



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ABSTRACT

Flubendiamide (FBD) is a novel diamide insecticide extensively used with potential human health hazards. This research aimed to examine the effects of FBD on PrEC prostate epithelial cells, including Oxidative stress, pro-inflammatory responses, modifications in the expression of oncogenic and suppressor miRNAs and their target proteins, disruption of the cell cycle, and apoptosis. Additionally, the research investigated the potential alleviative effect of T-SeNPs, which are selenium nanoparticles biosynthesized by *Trichoderma aureoviride*, against the toxicity induced by FBD. Selenium nanoparticles were herein synthesized by *Trichoderma aureoviride*. The major capping metabolites in synthesized T-SeNPs were Isochiapin B and Quercetin 7,3′,4′-trimethyl ether. T-SeNPs showed a spherical shape and an average size between 57 and 96.6 nm. FBD exposure (12 μM) for 14 days induced oxidative stress and inflammatory responses via overexpression of NF-κB family members. It also distinctly caused upregulation of miR-221, miR-222, and E2F2, escorted by downregulation of miR-17, miR-20a, and $P27^{kip1}$. FBD encouraged PrEC cells to halt at the G_1/S checkpoint. Apoptotic cells were drastically increased in FBD-treated sets. Treatment of T-SeNPs simultaneously with FBD revealed its antioxidant, anti-inflammatory, and antitumor activities in counteracting FBD-induced toxicity. Our findings shed light on the potential FBD toxicity that may account for the neoplastic transformation of epithelial cells in the prostate and the mitigating activity of eco-friendly synthesized T-SeNPs.

1. Introduction

Flubendiamide (FBD), (N^2- [1,1- dimethyl-2-(methylsulfonyl) ethyl]-3-iodo-N^1-[2-methyl-4- [1,2,2,2-tetrafluoro-1 (trifluoromethyl) ethyl] phenyl]-1,2- benzene dicarboxamide), is a relatively new phthalic acid diamide insecticide. The unique property of this compound is its aptitude to stimulate ryanodine receptors (RyRs), which are intracellular Ca^{2+} channels sensitive to ryanodine. This results in an increase in Ca^{2+} inflow into the cell and induces contraction of the skeletal muscles of insects (Das et al., 2017). It is considered safe for non-target since it does not activate mammalian RyRs; therefore, it is ubiquitously utilized worldwide to counter agricultural and domestic insects (Al-Mohaimeed et al., 2022). However, its excessive use may pose potential health hazards due to its slow degradation; FBD residues can persist on crops at harvesting time. Alarmingly, their accumulation in the body, even in small quantities, can adversely impact human health (Mandil et al., 2021). In a reproductive toxicity study, male rats subjected to 200 mg/kg of FBD showed a substantial decrease in sperm headcount per testis (Mandil et al., 2016). Mandil et al. reported that after 12 h in FBD-treated splenocytes, there was an increase in the frequency of micronuclei emergence (Mandil et al., 2020).

The prostate, an indispensable accessory organ of the male reproductive system, maintains the lubrication of seminal fluid and sperm nourishment, stimulating sperm motility and capacity (Verze et al., 2016). As such, it is vital to male fertility (Corti et al., 2022). Prostate cancer (PCa) is the most prevalent solid tumor among males and ranks second in terms of mortality rate (Siegel et al., 2021). Its etiology remains unknown, but it is significantly prevalent among farmers residing in regions with high insecticide exposure (Pardo et al., 2020).

Oxidative stress is characterized by an imbalance between the production and elimination of reactive oxygen species (ROS), which is caused by hyperactive signaling pathways (Kim et al., 2005; Hanahan and Weinberg, 2011). Oxidative stress from pesticide exposure may promote carcinogenic mutations (Tebourbi et al., 2011). Inflammation develops as an immediate and critical defense mechanism when the host is invaded or tissue is damaged. Sustained inflammation can lead to chronic inflammation, potentially increasing the organism's susceptibility to various chronic diseases, such as cancer (Lin et al., 2007). Continuous production of pro-inflammatory mediators and ROS may exacerbate genomic instability and promote the activation of a multitude of transcription factors, including the critical tumorigenesis-related nuclear factor kappa B (NF-κB) (Federico et al., 2007; Zhang et al., 2009).

The NF-κB family comprises transcription factors regulating apoptosis, cell proliferation, differentiation, and survival. These factors include nuclear factor-κB subunit 1 (NF-κB1) and nuclear factor-κB subunit 2 (NF-κB2), REL proto-oncogene nuclear factor-κB subunit (REL), RELA nuclear factor-κB subunit (RelA), and RELB proto-oncogene nuclear factor-κB subunit (RelB) (Rajendrasozhan et al., 2010). NF-κB activation has been identified as a factor in prostate cancer tumor progression, metastasis, and inflammation-associated tumor promotion (Luo et al., 2005; Hoesel and Schmid, 2013; Jin et al., 2013; Nguyen et al., 2014).

The activation of NF-κB is also responsible for the direct regulation of pro-inflammatory cytokine production, specifically tumor necrosis factor-alpha (TNF-α) and interleukin-1β (IL-1β) (Chen et al., 2018). Chronic inflammation evoked by pesticides can result in the secretion of proliferative cytokines (TNF-α, IL-1β, IL-8, and IL-6), thereby facilitating the growth of malignant cells (Grivennikov and Karin, 2011; Mokarizadeh et al., 2015).

Small noncoding RNAs (microRNAs) comprise a class of RNAs that regulate a broad spectrum of biological processes (Kloosterman and Plasterk, 2006; Bartel, 2009). As oncomiRs, miR-221 and miR-222 (miR-221/-222) are involved in the pathogenesis of PCa (Sun et al., 2009a, 2009b, 2014). Furthermore, miR-17 and miR-20a (miR-17/-20a) have been identified as suppressor miRNAs of PCa (Ottman et al., 2014).

Among the factors whose dysregulation was strongly associated with the development of PCa were the cyclin-dependent kinase inhibitor $p27^{Kip1}$ and E2F2 proteins. E2F2, a factor belonging to the E2F family of transcription factors, has been reported as a miR-17/20a target gene (Sylvestre et al., 2007) and possesses a potent oncogenic capacity and can facilitate the progression of the cell cycle (Dimova and Dyson, 2005). $P27^{kip1}$ is the target protein for miR-221/222 (Galardi et al., 2007). Previous studies have demonstrated that low or absent $P27^{Kip1}$ expression is linked to advanced tumor grade of PCa (Macri and Loda, 1998; Tsihlias et al., 1998).

The cell cycle is a fundamental process that occurs during the division of eukaryotic cells. At distinct cell cycle phases, checkpoints regulate the proliferation of healthy cells (Ekholm-Reed et al., 2004). Constitutive mitogenic signaling and mutations in tumor suppressor genes and proto-oncogenes contribute to the dysregulation of the cell cycle and uncontrolled proliferation that characterize the process of tumorigenesis (MacLachlan et al., 1995). Apoptosis is an orchestrated cell death regulated by various signals and metabolic processes (Aboubakr et al., 2021). The disruption of apoptosis can promote the initiation and progression of the tumor (Lowe and Lin, 2000).

Nanotechnology has garnered significant global interest due to its prospective applications in numerous sectors, including medicine (Shirsat et al., 2015; Basnet et al., 2018). Selenium nanoparticles (SeNPs) exhibit chemical, physical, and biological properties (Aref and Salem, 2020; Salem et al., 2021). SeNPs have significant biological applications as antimicrobial, antioxidant, and anticancer activity

(Thakkar et al., 2010; Hashem et al., 2021).

A wide array of techniques exist for synthesizing SeNPs, including physical, chemical, and biological-physical approaches (Chaudhary and Mehta, 2014; Weng et al., 2019). On the other hand, specific techniques are costly, necessitate using hazardous substances, and entail laborious, complicated, and unsustainable protocols. Therefore, chemical and physical processes are regarded less favorably than biological ones (Skalickova et al., 2017). Preferably, fungi secondary metabolites present in cell filtrate are utilized as reducing and encapsulating agents in a straightforward and expeditious approach to produce metal nanoparticles in an environmentally friendly manner (Bilesky-José et al., 2021; Raja et al., 2021). This synthesis method is ecologically sustainable, biodegradable, one-step, economical, and requires reduced reaction time and lower solvent usage.

Among filamentous fungi, species of *Trichoderma* are multifunctioning fungi found in diverse environments, typically forest or agricultural soils (Zin and Badaluddin, 2020). Previous studies have documented that SeNPs can be generated more from *Trichoderma* culture filtrate (Nandini et al., 2017; Hu et al., 2019). The biogenic synthesis of SeNPs by utilizing six species of *Trichoderma* has been recently referred to as "Trichogenic" (Nandini et al., 2017).

Trichoderma species produce numerous volatile organic compounds (VOCs), which possess various biological and chemical attributes, including antioxidants and antitumor potential (Saravanakumar et al., 2019). Recent studies indicated several compounds extracted from *T. atroviride* had a high anti-prostate cancer potential (Saravanakumar et al., 2019) and were cytotoxic against different cancer cell lines (Li et al., 2020).

In this study, we used PrEC prostate cells to investigate the reproductive toxicity of FBD. The prostate is a critical organ in the male reproductive system, making it a relevant model for examining reproductive effects. Furthermore, PrEC epithelial cells could be transformed into pre-neoplastic lesions and invasive carcinoma at the final stages through genetic and epigenetic alterations (Zhou et al., 2016).

The current study assessed the toxic effects of FBD on crucial pathways in the process of prostate tumorigenesis, such as oxidative stress, pro-inflammatory responses, oncogenic and suppressor miRNA expressions and their target proteins, cell cycle dysregulation, and apoptosis. These molecular transformation markers describe distinctive features that transformed cells acquire during the oncogenic process of prostate carcinogenesis. Furthermore, the present study explored the ameliorative role of SeNPs biosynthesized by *T. aureoviride* (T-SeNPs) against toxicity instigated by FBD.

2. Materials and methods

2.1. Biosynthesize of SeNPs by T. aureoviride

2.1.1. T. aureoviride source and taxonomy

In the present study, *T. aureoviride* was derived from previous phylogenetic analysis and identification of 40 strains by (Hewedy et al., 2020). To confirm the prior identification of the fungal strain (*T. aureoviride*, MH908501), the *TEF1* gene was amplified using two primers (Eurofins) named EF1-728 F (5'CATCGAGAAGTTCGAGAAGG3') and TEF1 R (5'GCCATCCTTGGAGATACCAGC3') as previously described by (Hewedy et al. 2020).

2.1.2. T. aureoviride inoculum preparation

A pure culture of the isolate *T. aureoviride* fungus was obtained by aerobically inoculating *T. aureoviride* on Potato Dextrose Agar (PDA) using the protocol of Samuels et al. (2002). (For details, see Appendix A, Supplementary material).

2.1.3. Extraction of Trichoderma's metabolites

The secondary metabolites of *T. aureoviride* were extracted from its cell-free filtrate following previous techniques of Saravanakumar et al. (2015); Saravanakumar and Wang (2018). (For details, see Appendix B, Supplementary material). To identify the chemical composition, the *T. aureoviride* cell-free filtrate was eluted with 80% methanol.

2.1.4. Preparation of SeNPs and T-SeNPs

SeNPs were prepared using the technique of (Vahdati and Tohidi Moghadam, 2020). (For details, see Appendix C, Supplementary material). The generation of T-SeNPs was carried out following (Nandini et al. 2017) with some modifications. The production of nanoparticles was started by adding 40 ml of *T. aureoviride* culture filtrate to 70 ml of sterile distilled water that contained 25 mM sodium selenite to make it up to 110 ml. The reaction mixture was shaken at 150 rpm at 28 ° C for 7 days. The appearance of a change in reaction mixture color was the first visible indicator of nanoparticle production. After 7 days, the mixture of reactions was gathered, and the nanoparticles were precipitated by centrifuging for 10 min at 10,000 rpm. The precipitate was refined after being rinsed with double distilled water (Zhang et al., 2011). Appropriate controls were maintained throughout the trial.

2.1.5. Characterization of synthesized T-SeNPs and SeNPs

The preparation of T-SeNPs and SeNPs for characterizations was performed according to (Hu et al., 2019). Fourier-transform infrared spectroscopy (FTIR) (PerkinElmer, the UK) was used to identify the interactions between functional groups and chemical composition at the 400–4000 cm-1 scanning range. The nano-powders crystalline structure and phase identification were investigated utilizing an X-ray Diffractometer (XRD) (SHIMADZU, XRD-6000) equipped with Copper Kα radiation. (For details, see Appendix D, Supplementary material). The synthesized T-SeNPs' surface charge and particle size were determined utilizing a Nanotrac-Wave II Zetasizer (MICROTRAC, USA). The size and morphological characteristics of the T-SeNPs were subsequently evaluated using Transmission Electron Microscopy (TEM) (JEM-2100, JEOL, Japan). (For details, see Appendix E, Supplementary material).

2.1.6. Metabolite profiling through GC-MS analysis

To explore the metabolites that were found in the cell filtrate of *T. aureoviride* as well as those that are implicated in the generation of SeNPs, a metabolite profiling procedure was conducted utilizing GC-MS (Trace GC-TSQ mass spectrometer, Thermo Scientific, Austin, TX, USA). (For details, see Appendix F, Supplementary material). The identity of bioactive compounds was determined using the National Institute Standards and Technology (NIST) database and WILEY mass spectrum libraries of the GC-MS system with over 62,000 patterns.

2.2. In vitro testing

2.2.1. Chemicals

The commercial formulation of FBD (Takumi®) (20% WDGs) was purchased from Samtrade Company, Cairo, Egypt.

2.2.2. Cell lines

Human primary prostate epithelial cells (PrEC) were purchased from the American Type Culture Collection (ATCC) and cultivated using Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10 μg/mL of insulin, 10% fetal bovine serum (FBS), and 1% antibiotics (penicillin-streptomycin). The cells were retained in a 37 °C humidified atmosphere of 5% CO_2.

2.2.3. MTT assay

MTT assay (Sigma-Aldrich) was utilized to assess the impact of FBD, SeNPs, and T-SeNPs on the viability of PrEC cells. First, FBD, SeNPs, and T-SeNPs were diluted with a DMEM medium. Briefly, PrEC cells were sown with a density of 1.8×10^3 in 96-well cell culture microplates (Corning Inc., USA). Each microplate was incubated at 37 °C with different concentrations of FBD (210, 180, 120, 100, 80, 60, and 30 μM).

In addition, the cells received the same concentrations of SeNP and T-SeNP, which were as follows: 280, 250, 220, 190, 150, 110, 90, and 60 μl/ml.

These concentrations were selected to ensure a comprehensive representation of the effects from those that are undetectable (in comparison to the negative controls, *i.e.*, 0%) to those that result in 100% mortality. Microplate without any treatment was considered as a control. The medium was withdrawn after 24 h of incubation, and each well received 0.5 mg/ml of MTT in phosphate-balanced solution (PBS), which was then incubated at 37 °C. Cells were incubated for 4 h. The changes were measured using ROBONIK P2000 Elisa Reader with an optical density of 570 nm. The cell viability percentage is expressed as (absorbance of treated cells/absorbance of untreated cells) × 100 %. This equation was used to measure the sensitivity of cells to FBD, SeNPs, and T-SeNPs. The half-maximal inhibitory concentration (IC_{50}) value is the concentration that results in 50% of cells dying.

In the current study, we have selected the highest concentration of 12 μM of FBD, which is approximately 10 % of the IC_{50} value determined through cytotoxicity analysis. This selection ensured that FBD would not directly impact PrEC cells' viability. Furthermore, the selected concentration of FBD mimicked the conditions encountered in daily life. The choice of this concentration was based on findings from prior studies, which indicated that *in vitro* concentrations of 10–50 μM provide an accurate representation of real-life exposure scenarios to insecticides such as organophosphorus (Buratti et al. 2002, 2003, 2005; Buratti and Testai, 2007).

Considering the increased environmental persistence of FBD, which does not dissipate promptly into the environment and has the potential to induce chronic effects in a manner comparable to that of persistent compounds, such as organophosphates (Das et al., 2017; Jadhav and David, 2017), the same exposure threshold was utilized in this investigation to mimic environmental exposure to FBD. Although this methodology might not have broad applicability to all pesticide types, it provided valuable insights for our investigation's preliminary stage.

2.2.4. Exposure conditions

The PrEC cells were planted at a density of 5×10^3 cells/cm^2 in the 12-well cell culture plates. Repeated exposure to FBD was conducted in this study to assess the toxicity of FBD over an extended period and mimic real-world exposure to pesticides. Over 14 days (Kramer et al., 2015), the seeded cells were treated with FBD, SeNPs, and T-SeNPs as follows: group 1: cells were treated with FBD 12 μM, group 2: cells were treated with SeNPs 50 μl/ml (Hu et al., 2019), group 3: cells were treated with T-SeNPs 50 μl/ml (Hu et al., 2019), group 4: cells were treated with FBD 12 μM, then treated with SeNPs 50 μl/ml, group 5: cells were treated with FBD 12 μM, then treated with T-SeNPs 50 μl/ml, and group 6: cells without any treatment considered as control. Cell culture media was changed with fresh FBD, SeNPs, and T-SeNPs suspensions every 2 or 3 days, with no wash steps between treatments. All cells were incubated at 37 °*C* in 5% CO_2.

2.2.5. Oxidative stress analysis

The microscale analysis of the level of malondialdehyde (MDA), content of reduced glutathione (GSH), superoxide dismutase (SOD), glutathione peroxidase (GPx), glutathione reductase (GR), glutathione -*S*- transferase (GST), total antioxidant capacity (TAC), protein carbonyl and catalase (CAT) activity was performed in the PrEC cells supernatants in control and treated groups. The measurements were conducted using commercial kits that adhered to the manufacturer's instructions (Biodiagnostic, Giza, Egypt).

The MDA, GSH, SOD, CAT, GPx, GR, GST, TAC, and protein carbonyl were measured according to (Ohkawa et al., 1979; Beutler et al., 1963; Nishikimi et al., 1972; Aebi, 1984; Paglia and Valentine, 1967; Goldberg and Spooner, 1987; Habig et al., 1974; Koracevic et al., 2001; Levine et al., 1990), respectively. Each experiment was conducted in triplicate.

2.2.6. The quantitative RT-PCR

Following the manufacturer's instructions, a miRNA easy extraction kit (QIAGEN, Germany) was used to isolate total RNA from treated and untreated PrEC cells. To evaluate the concentration and guarantee the purity of the samples' RNA, a Nanodrop instrument (Thermo Scientific, USA) was employed. Using a miScript II RT kit, complementary DNA (cDNA) was produced by reverse transcription (QIAGEN, Germany). Real-time PCR was executed utilizing the ROCHE Real-time PCR light cycler detection equipment with the SYBR Green master mix (Bio-Rad Laboratories, USA).

Gene primers of inflammatory cytokines and miRNAs were designed using the National Center for Biotechnology Information (NCBI) database. Primers for apoptotic genes, including *Caspase-3*, *Bax*, *P53, Caspase-9,* and *Bcl-2,* were utilized as previously outlined (Al-Fatlawi et al., 2015). The expression levels of miRNAs and mRNAs were normalized to the internal references of U6snRNA (Song et al., 2015) and glyceraldehyde-3-phosphate dehydrogenase (*GAPDH*), respectively, and calculated using the $2^{-\Delta\Delta CT}$ technique (Livak and Schmittgen, 2001). The forward and reverse primer sequences of miRNAs and mRNAs are listed in Table S1. Three repetitions of each experiment were performed.

2.2.7. Western blotting

The total protein of the treated and untreated PrEC cells was extracted using a lysis buffer. A 20 μg protein was isolated on SDS-PAGE and then transferred to a membrane. Afterwards, the membrane was blocked in TBST for 2 h at room temperature, utilizing 5% nonfat dry milk. The membrane was incubated overnight at 4 °C with primary antibodies $P27^{kip1}$, E2F2, and β-actin. The blots were then washed three times with TBST. The chemiluminescent Western ECL substrate (PerkinElmer, Waltham, MA) was applied to the blot according to the manufacturer's recommendation.

2.2.8. Cell cycle regulation

Treated and untreated PrEC cells underwent trypsinization, centrifugation at 300ˆ g for 5 min, and subsequent rinsing in ice-cold PBS. Following this, the cells were resuspended in 1 ml of cold ethanol 70% (v/v) and incubated at 4 °C for at least 2 h. Following two rinses with 2 ml PBS, the cells were incubated for 15 min. After centrifugal, the cells were stained with 0.5 ml propidium iodide solution (PI). Cells were mixed and incubated in dark conditions for 30 min at 37 °C. Finally, the DNA content was measured by a flow cytometer (BD FACSCalibur™) with an excitation source set at 488 nm and an emission source set at 525 nm.

2.2.9. Apoptosis examination

Apoptotic PrEC cells have been evaluated by labeling with FITC-Annexin and PI in accordance with the manufacturer's protocol (BD Biosciences, San Jose, CA, USA). The PrEC cells were gathered and rinsed with PBS. They were then resuspended in 100 μL of a binding buffer containing 5 μL of PI and annexin V-FITC. The mixture was permitted to react at room temperature for 10 min without exposure to light. The percentage of cells in each quadrant was identified and analyzed using a BD FACSCalibur™ flow cytometer.

2.3. Statistics

All assays were performed in triplicates. Statistical tests were executed utilizing SPSS software (version 21.0; SPSS Inc., Chicago, IL, United States). A one-way ANOVA, followed by Duncan's multiple comparisons test, was used to compare the various data sets. The findings were presented as mean ± SD. When $p \leq 0.05$, values were deemed statistically significant. GraphPad PRISM 9.0 software (Graph-Pad Software, San Diego, USA) was utilized to calculate the IC_{50} and visualize data.

lines, including DU-145 and PC-3, exhibit constitutive expression of *NF-kB1* and *NF-kB2* genes. In contrast, normal human prostate epithelial cells exhibit negligible activation of *NF-kB* genes (Gasparian et al., 2002; Nguyen et al., 2014; Dominska et al., 2017). In addition, *NF-kB1* expression is crucial for both the early and advanced stages of PCa (Dominska et al., 2017). The capabilities of cancer cells to migrate and invade are regulated by the RelB gene (Lessard et al., 2005; Xu et al., 2009).

Prostate cancer cells such as PC3, DU-145, and LNCaP exhibited increased expression of *RelA*, *RelB* (Josson et al., 2006; Hatano et al., 2011), and *C-Rel* (Dominska et al., 2017). Previous studies reported that human prostate cancer cells PC3 and DU145 cells express *IL-8* (Lee et al., 2004; Araki et al., 2007; Singh and Lokeshwar, 2009) and *IL-6* (Xu et al., 2017; Wang et al., 2022). *IL-1β* and *TNF-α* expressions are increased in LNCaP prostate epithelial cells (Safari et al., 2020). In this study, pro-inflammatory cytokines, including *NF-kB1*, *NF-kB2, RelA*, *RelB*, *C-Rel*, *TNF-α*, *IL-1β*, *IL-8,* and *IL-6* were upregulated in PrEC cells treated with FBD, suggesting the presence of an inflammatory response. FBD stimulated NF-κB due to oxidative stress (Siomek, 2012).

Substantial evidence has proven the involvement of miRNAs in regulating various cellular biological mechanisms, including development, cell proliferation, apoptosis, and tumorigenesis (Catellani et al., 2021; Li et al., 2018, 2022; Qiu et al., 2022). It is known that miR-221/222 is overexpressed in PC3 prostate cancer epithelial cells (Shao et al., 2018; Alwyn Dart et al., 2019). In addition, miR-17/-20a is downregulated in LNCaP prostate cancer epithelial cells (Ottman et al., 2014, 2016). However, when overexpressed in non-tumor cells, it has anti-proliferative, adhesive, and anti-migratory effects (Ottman et al., 2016).

The current study observed that exposure to FBD resulted in an upregulation of miR-221/222 expression and a significant downregulation of miR-17/20a. Based on our findings, it appears that the modification of miRNA transcription could be a consequence of the activation of NF-κB of FBD induced by oxidative stress (Simone et al., 2009; Ebrahimi et al., 2020; Mandil et al., 2023). This activation results in an elevation of cytosolic free Ca^{2+} concentration and subsequently hinders the Ca^{2+} clearance system. Ultimately, this causes mitochondrial depolarization and cell dysfunctions (Salido, 2009; Kushawaha et al., 2020).

Failure of a cell to regulate its proliferation and growth is a distinctive hallmark of cancer (Dong et al., 2010). Proteins E2F2 and $p27^{kip1}$ are crucial for controlling the cell cycle. The expression of $p27^{kip1}$ and miR-221/222 is inversely correlated with each other in primary prostate cancer (Galardi et al., 2007; Sun et al., 2014). The $p27^{kip1}$ expression was impeded in prostate cancer epithelial cell lines 22Rv1 and LNCaP (Galardi et al., 2007; Mercatelli et al., 2008).

On the other hand, E2F2 regulates various molecular mechanisms, including cell cycle, DNA repair, cellular proliferation, and cell death (Chen et al., 2009). It has substantial oncogenic potential and can accelerate the cell cycle, thus promoting cell proliferation at twice the rate of control cells (Dong et al., 2010). It has been reported that E2F2 was upregulated in the PC3 prostate cancer epithelial cell line and, even more, correlated well with cancer progression and prognosis (Tyagi et al., 2002; Dong et al., 2010). The current investigation results revealed that PrEC cells exposed to FBD displayed a notable decrease in $p27^{kip1}$ level and an increase in E2F2 level, inducing cell cycle deregulation. These results have emerged owing to the oxidative stress induced by FBD (Quintos et al., 2010; Wang et al., 2021).

Therefore, flow cytometry and PI labeling were employed to validate the cell cycle deregulation and apoptosis induced by FBD. The main goal of cell cycle analysis is to quantify the amount of DNA present in each cell cycle phase (Dong et al., 2010). At the G1/S checkpoint, the cell cycle of LNCaP and DU145 prostate cancer epithelial cells was halted (Galardi et al., 2007; Roy et al., 2008; Van Duijn et al., 2010; Han et al., 2022). The present inquiry unveiled that exposure to FBD instigated a halt in the progression of the cell cycle of PrEC cells at the G1/S checkpoint. The observed outcomes could potentially be attributed to FBD-induced oxidative stress. An overabundance of ROS causes permanent damage to cellular constituents, impeding the progression of the cell cycle (Metallo and Vander Heiden, 2013). Moreover, the halting of the cell cycle can be ascribed to a multitude of factors, encompassing the increases of E2F2 levels, the reduction in $p27^{kip1}$ levels, and the overexpression of miR-221/-222 through FBD exposure (Galardi et al., 2007; Roy et al., 2008; Nogueira et al., 2008; Moon et al., 2010; Nedeljkovic et al., 2018; Han et al., 2022).

The intrinsic apoptotic pathway is initiated by a pro-apoptotic stimulus that induces mitochondrial membrane disruption, which leads to the activation of caspases (Xiong et al., 2014). The Bcl-2 family of proteins regulates the mitochondrial pathways of apoptosis. This family is divided into anti-apoptotic proteins, such as Bcl-2 and pro-apoptotic proteins, such as Bax, which are responsible for the decision to initiate apoptosis in cells (Borner, 2003). Further, activating the tumor suppressor protein P53 may facilitate the apoptotic process through either transcription-independent mechanisms or activating the pro-apoptotic protein (Fridman and Lowe, 2003; Jeffers et al., 2003). The dysregulation of apoptosis may facilitate oncogenesis (Fulda, 2009).

In the present research, cellular apoptosis (early and late) was considerably instigated after FBD intoxication. Moreover, FBD upregulated the gene expression of *P53*, *Bax*, *Caspase-9,* and *Caspase-3* while simultaneously downregulating the gene expression of *Bcl-2*, activating apoptosis. The observed result could potentially be ascribed to the G1/S checkpoint arrest triggered by FBD exposure, which permits cells to proceed along the apoptotic pathway (Hunter and Pines, 1994), as well as the oxidative stress elicited by FBD (Nogueira et al., 2008; Moon et al., 2010; Mandil et al., 2023).

The outcomes achieved here align with those of earlier studies revealing that FBD exposure at 40 μM for 12 h can cause apoptosis in thymocytes of male Wistar rats (Mandil et al., 2023). Previous *in vivo* investigations have divulged that FBD significantly increased the mRNA levels of *P53*, *Caspase-3*, *Caspase-9*, and *Bax* in the liver of zebrafish (Meng et al., 2022). Additionally, chlorantraniliprole, a diamide insecticide, inhibited the *Bcl-2* expression in the liver of zebrafish (Meng et al., 2022).

T. aureoviride was selected to investigate the attenuation effects of synthesized T-SeNPs conjugate on alleviating FBD-induced toxicities in PrEC cells. Thus, in the present study, T-SeNPs were generated from Se^{+} using *T. aureoviride* cell filtrate (microbe's cell component) (Nandini et al., 2017) rather than the entire microorganism because when using live microorganisms, the growth stage and incubation time significantly impact nanoparticle size and characteristics (Fernández-Llamosas et al., 2016). The presence of T-SeNPs can be detected through a color transition (brick orange) that occurs throughout the reaction, as documented by Nandini et al. (2017). Multiple studies have revealed the synthesis of SeNPs utilizing ascorbic acid as the reducing agent (Malhotra et al., 2014).

Hydrodynamic size, zeta potential, and PDI are key indices that characterize nanoparticles (Zhao et al., 2016). The hydrodynamic sizes of T-SeNPs and SeNPs were 206.4 and 88.6 nm, respectively, exhibiting a narrower size distribution. Lower PDI values signify a more uniform size distribution of nanoparticles (Mi et al., 2021). Owing to the greater zeta potential of the produced T-SeNPs, the electrostatic repulsions between them are increased, making them more stable; this stability may be due to the stabilization of SeNPs by *T. aureoviride* cell filtrate biomolecules.

In the present investigation, the XRD data of T-SeNPs revealed a dual phase consisting of amorphous and nano-crystalline nanoparticles. In contrast to SeNPs, these nanoparticles exhibited noisy characteristics and broad peaks devoid of distinct, sharp reflections. These findings suggest that the T-SeNPs engaged in interactions with biomolecules found in the fungus cell filtrate (Nandini et al., 2017). This characteristic feature likely influenced the interactions in our study, as the amorphous and nano-crystalline nature of T-SeNPs could enhance their reactivity

and interaction with cellular components. Consequently, this might have contributed to the observed enhancement of T-SeNPs activity.

The FT-IR spectra acquired for SeNPs biosynthesized by *T. aureoviride* identified the presence of carbonyl, ketonic, hydroxyl, amino, phenolic, and flavonoid functional groups, which are utilized in the production of T-SeNPs. The biomolecules are sustained by the metabolites generated by *T. aureoviride*, which are responsible for the presence of these functional groups. The aforementioned functional groups exhibit metal-binding capabilities and serve as capping agents and stabilizers for the Se nanoparticles, thereby impeding their aggregation (Prasad and Selvaraj, 2014; Sabandar et al., 2017; Baranović and Šegota, 2018; Liu et al., 2020; Hosseinpour et al., 2022).

This finding aligns with the research carried out by Nandini et al. (2017) and Ogunleye et al. (2022), which illustrated that nanoparticles produced by *Trichoderma* spp. were surrounded by proteins that potentially accounted for their stability, as determined by FI-TR spectrum analysis. Moreover, the bio-reduction of SeNPs can be attributed to the hydroxyl and carbonyl functional groups that are currently present.

The morphology and size of the T-SeNPs and SeNPs generated in the present study were spherical nanoparticles well dispersed without agglomeration in the TEM micrographs, with average particle sizes less than 100 nm. Characters of SeNPs generated were consistent with earlier studies on synthesizing SeNPs from fungal sources (Nandini et al., 2017; Hu et al., 2019; Zhang et al., 2019). Thus, the current findings unequivocally demonstrated the varying capacity of *T. aureoviride* to produce SeNPs. Prameela Devi et al. also observed this finding when they assessed 75 strains of *Trichoderma* spp. pertaining to five unique species for silver nanoparticle synthesis (Prameela Devi et al., 2013).

A GC-MS examination was conducted to identify the metabolites found on the T-SeNPs. Out of a total of 25 metabolites that were identified in the cell filtrate of *T. aureoviride*, 5 were determined to be involved in the coating of SeNPs. The major identified metabolites were isochiapin B and quercetin 7,3′,4′-trimethyl ether. These findings were supported by FT-IR analysis of T-SeNPs. These results were due to the adsorption of these constituents on the nanoselenium surface (Siakavella et al., 2020).

Isochiapin B has been reported to possess antitumor, antimicrobial, and antioxidant activity properties (Gach et al., 2015; Sharma et al., 2021). Moreover, quercetin 7,3′,4′-trimethyl ether is one of the quercetin derivatives, which is a ubiquitous flavonoid that exhibits pharmacological characteristics as an antitumor, antioxidant, and anti-inflammatory (Kalender et al., 2012; Hassan et al., 2019). Earlier studies described quercetin's efficacy in synthesizing SeNPs (Mittal et al., 2014).

Quercetin inhibited NF-kB activation in primary cultured thymocytes and splenocytes of rats treated with monosodium glutamate, thereby decreasing the gene expression of *IL-1β*, *TNF-α*, and *IL-6* (Das et al., 2024). Moreover, quercetin has antioxidant properties through multiple mechanisms, such as its ability to scavenge free radicals, quench singlet oxygen, and donate hydrogen compounds (Wilms et al., 2008).

It increased GSH quantity and the activities of CAT, SOD, and GPx while decreasing MDA levels in HepG2 cells (Yarahmadi et al., 2021). The administration of quercetin resulted in a decrease in the levels of protein carbonyl and an increase in the TAC of rat testicular cells (Benko et al., 2020). Quercetin increased GST, GR, and TAC activities in the testes and epididymis of dichlorvos-exposed rats (Bukunmi Ogunro, 2023).

Quercetin inhibits oncogenes or increases tumor suppressor genes by altering miRNA expressions (Li et al., 2014; Farooqi et al., 2018). Furthermore, quercetin mediated the upregulation of $P27^{kip1}$ and downregulation of E2F2 and triggered the halt of the cell cycle during the G_2/M phase in several cancer cells (Mu et al., 2007; Jeong et al., 2009; Huan et al., 2012). Quercetin also substantially mitigated the effects of cellular damage and apoptosis provoked by various insecticides (Zeng et al., 2021). It exhibits anti-apoptotic properties through multiple mechanisms, such as its ability to scavenge free radicals, quench singlet oxygen, and donate hydrogen compounds (Wilms et al., 2008).

The treatment of quercetin caused a reduction in the expression of *Caspase-3* and *Bax* genes, as well as an increase in *Bcl-2* expression in the lung tissues of cypermethrin-exposed rats (Ileriturk et al., 2022). Hepatic *P53* and *Caspase-9* gene expressions were substantially reduced in fenitrothion-intoxicated foetal rats following quercetin treatment (Ibrahim et al., 2021).

Our findings elucidated that the ameliorative role of T-SeNPs in the molecular and cellular toxicity in the PrEC cells induced by FBD is more pronounced than the SeNPs. The cytotoxicity of T-SeNPs was lower on PrEC cells than SeNPs. These findings paralleled with those of Hu et al. (2019), who stated that SeNPs produced by culture filtrates of *T. harzianum* did not exhibit cytotoxicity towards the GES-1 gastric epithelial cell line, LX-2 human hepatic stellate cell line, and HIEC intestinal epithelial cell line.

In this work, T-SeNPs or SeNPs decreased MDA and protein carbonyl levels, restored the GPx, CAT, GR, TAC, GST, and SOD activities, and augmented the GSH amount in the FBD-intoxicated group. These results indicate that T-SeNPs or SeNPs potentially scavenge free radicals and exert an antioxidative effect. Earlier *in vivo* studies have revealed that the administration of SeNPs to cypermethrin-treated rats resulted in a significant decrease in hepatic MDA levels and a considerable increase in GSH, SOD, and CAT levels (Abdou and Sayed, 2019).

The activities of GST and GR were enhanced in male fetuses of rats treated with SeNPs (Manojlović-Stojanoski et al., 2022). The activity of GR was elevated in the brain tissues of cadmium-exposed rats (Al Kahtani, 2020). SeNPs administration reduced protein carbonyl levels in the ovary tissue of female rats intoxicated with cadmium (Choopani et al., 2023). The activity of TAC in buffalo rat liver (BRL) cells was elevated by SeNPs at concentrations of 1 and 12 μM (Wang et al., 2020).

The co-administration of T-SeNPs or SeNPs with FBD lowered the upregulating mRNA of *NF-kB* family members, *IL-6*, *TNF-α*, and *IL-1β*, suggesting the presence of anti-inflammatory properties. Additionally, the present study revealed that the post-treatment of T-SeNPs or SeNPs remarkedly decreased elevated expression of miR-221/222 and boosted decreased expression of miR-17/20a in FBD-exposed cells, indicating antitumor efficacy. The T-SeNPs or SeNPs substantially recovered $p27^{kip1}$ and E2F2 expressions in FBD-intoxicated cells. On the other hand, both SeNPs and SeNPs-T extracts inhibited G_2/M phase progression in FBD-treated cells; however, the fraction of cells inhibited by T-SeNPs treatment was greater, implying an anti-proliferative effect. The halt of the cell cycle at the G_2/M phase is considered essential antitumor target links, which have now become hotspots for investigation in developing several antitumor therapies (Venkatadri et al., 2016). Consequently, this research suggests that the antitumor and antioxidant mechanisms of T-SeNPs are also focused on cell-cycle arrest.

Another noteworthy finding was that T-SeNPs significantly attenuated the apoptotic rate in FBD-exposed cells. Moreover, T-SeNPs notably decreased the mRNA levels of *Caspase-3*, *Caspase-9*, *Bax*, and *P53*, while increasing the mRNA level of *Bcl-2* in the FBD-intoxicated group. Our findings are consistent with those of previous research, which demonstrated that the administration of SeNPs could reduce the elevated expression of *Caspase-3*, *Caspase-9*, and *Bax*, as well as increase the expression of *Bcl-2* in grass carp hepatocytes (L8824) that were treated with 4-*tert*-butylphenol (Cui et al., 2023). Previous *in vivo* studies have shown that SeNPs suppress the gene expression of intestinal *P53* in healthy mice (Sun et al., 2019).

In this study, PrEC cells exhibited apoptosis when treated with either T-SeNPs or SeNPs alone, although the apoptotic rate was lower with T-SeNPs. Furthermore, our findings demonstrated a considerable increase in *Caspase-3*, *Caspase-9*, *Bax*, and *P53* and a significant reduction in *Bcl-2* expression following treatment with either T-SeNPs or SeNPs. However, the changes in the expression of apoptosis-related genes were less pronounced with T-SeNPs. These findings may be attributed to the ability of

SeNPs to induce apoptosis through depleting mitochondrial membrane potential (Zhang et al., 2013).

Additionally, SeNPs could induce apoptosis through a mitochondria-mediated apoptotic pathway, dependent on Caspase-3 and Caspase-9 (Liao et al., 2015; Wang et al., 2020), and may also trigger apoptosis via P53 activation (Jiang et al., 2014). Quercetin may contribute to the reduction of apoptosis in response to T-SeNP treatment. These results align with previous research demonstrating the potential of SeNPs to induce apoptosis in human keratinocytes (HaCaT cells) (Kirwale et al., 2019). Additionally, the apoptotic rate of BRL cells is substantially increased following SeNPs at 48 μM for 24 h (Wang et al., 2020).

Following the findings of our GC-MS analysis, the antioxidant activity of T-SeNPs was due to the capping of quercetin and isochiapin B. Consequently, T-SeNPs exert amelioratory effects on the toxicity induced by FBD (Fig. S3). This beneficial action may be attributed to the ability of nanoparticles to enhance the stability and solubility of phytochemicals, strengthen their absorption, guard them against premature deterioration in the body, and extend the duration of their circulation (Wang et al., 2014). Moreover, nanoparticles rapidly garner momentum as an antitumor and antioxidant due to their excellent surface area to size ratio (Joshi et al., 2019; Samrot et al., 2022).

5. Conclusion

We conclude that repeated exposure of PrEC cells to FBD induced oxidative stress and pro-inflammatory response; this leads to chronic inflammatory reactions, altering oncogenic and suppressor miRNA and their target proteins. It also provoked cell cycle arrest at the G_1/S checkpoint and eventual apoptosis. Our findings also revealed that *T. aureoviride* could be employed for the mycosynthesis of SeNPs and exhibited antitumor, anti-inflammatory, and antioxidant properties against toxicities induced by exposure to FBD. Future studies comparing the effects of FBD exposure in cancer cell lines could provide further insights into the differential responses between normal and cancer cells, enhancing understanding of the broader implications of FBD toxicity and the ameliorative effects of T-SeNPs.

CRediT authorship contribution statement

Samah S. Arafa: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Sahar Badr El-Din:** Writing – review & editing, Visualization, Resources, Methodology, Investigation. **Omar A. Hewedy:** Writing – review & editing, Visualization, Resources, Methodology, Investigation. **Shimaa Abdelsattar:** Writing – review & editing, Visualization, Resources, Methodology, Investigation. **Sanaa S. Hamam:** Writing – review & editing, Visualization, Resources, Methodology, Investigation. **Asmaa F. Sharif:** Writing – review & editing, Visualization, Resources, Methodology, Investigation. **Reem Mohsen Elkholy:** Writing – review & editing, Visualization, Resources, Methodology, Investigation. **Ghada Zaghloul Shebl:** Writing – review & editing, Visualization, Resources, Methodology, Investigation. **Majid Al-Zahrani:** Investigation, Methodology, Resources, Visualization, Writing – review & editing. **Rasha Aziz Attia Salama:** Investigation, Methodology, Resources, Visualization, Writing – review & editing. **Afaf Abdelkader:** Writing – review & editing, Visualization, Resources, Methodology, Investigation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

List of abbreviations:

FBD	Flubendiamide.
PCa	Prostate cancer
SeNPs	Selenium nanoparticles
T-SeNPs	Nano-selenium synthesized by *Trichoderma aureoviride*.
PrEC	Human normal primary prostate epithelial cell lines
GC-MS	Gas chromatography-mass spectrometry
PDB	Potato Dextrose Broth
FT-IR	Fourier Transform infrared spectroscopy
TEM	Transmission Electron Microscopy
XRD	X-Ray Diffractometer
NIST	National Institute Standards and Technology
PDI	polydispersity index
ATCC	American Type Culture Collection
DMEM	Dulbecco's Modified Eagle Medium
FBS	Fetal bovine serum
PBS	phosphate-balanced solution
PI	Propidium iodide.
MDA	Malondialdehyde
GSH	Reduced glutathione
SOD	Superoxide dismutase
GPx	Glutathione peroxidase
GR	Glutathione reductase
GST	Glutathione -*S*- transferase
TAC	Total antioxidant capacity
CAT	Catalase

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.chemosphere.2024.143305.

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