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Research Paper

Effect of Physicochemical Factors on Amiodarone Toxicity in *Saccharomyces Cerevisiae*

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ABSTRACT

Background: Amiodarone (AMD) is an antiarrhythmic drug that induces idiosyncratic toxicity. Different physicochemical parameters could interact with its toxicity by affecting pharmacokinetics and pharmacodynamics. In the present study, we investigated the effects of temperature, pH, electrical current, and ultraviolet (UV) on the toxicity of this drug in the wild type BY4741 of *Saccharomyces cerevisiae.*

Methods: The percentage of growth and half inhibitory concentration (IC_{50}) of AMD under different conditions were calculated using GraphPad Prism after measuring yeast growth with a spectrophotometer.

Results: Based on the findings obtained, amiodarone alone decreased yeast growth in a dose-dependent manner and was accompanied by reduced CO_2 release, suggesting a possible role of fermentation in protecting cells from the drug's toxicity. Acidic pH increased the inhibitory effect of AMD on growth by lowering the IC_{50}, while basic pH decreased this effect by raising the IC_{50}. Toxicity also increased when cells were exposed to a temperature of 50 °C, indicating that yeasts were sensitized through stress induction. However, exposure to a low temperature of -20 °C had no effect. On the other hand, the growth inhibition of BY4741 was slightly reduced when irradiated by UV, indicating a possible effect on cell proliferation. A similar effect was observed in cells exposed to a voltage of 9 V, which increased the IC50. This may be due to the influence of current on AMD's membrane transporters.

Conclusion: Overall, pH, temperature, UV, and an electric current can modify the toxicity induced by AMD in yeast, indicating the possibility of the influence of physicochemical parameters on the toxicity of this idiosyncratic drug.

Keywords: Amiodarone, Chemical and physical Factors, Drug Toxicity, Growth, *Saccharomyces cerevisiae*

Introduction

Amiodarone (AMD) is a benzofuran-based antiarrhythmic agent that exerts its effects by disrupting membrane ion channels, primarily through alterations in lipid bilayer dynamics [1]. Its hepatotoxicity has been linked to idiosyncratic mechanisms [1]. In yeast models such as *Saccharomyces cerevisiae*, AMD toxicity varies with genetic background, suggesting strain-specific responses [2,3]. While pathological conditions have been implicated in modulating AMD toxicity [4], other intrinsic factors, such as age, sex, and circadian rhythms, also influence drug response [5].

Environmental physicochemical factors, including pH, temperature, and UV exposure, can significantly influence cellular behavior and drug interactions [6]. For instance, changes in pH can alter drug solubility and membrane permeability, thereby affecting absorption and distribution. Similarly, temperature shifts may impact enzymatic activity and membrane fluidity, modifying drug efficacy and toxicity. The UV radiation can induce photochemical changes in drug molecules, potentially enhancing or reducing their toxic effects [7].

Alterations in acid–base balance, particularly changes in pH, can significantly impact various pharmacological properties of drugs. These effects are evident in drug absorption from the gastrointestinal tract, distribution between plasma and tissues, and renal excretion patterns [8]. For example, acidification of the cell culture medium has been shown to reduce the cytotoxicity of doxorubicin—a chemotherapeutic agent—on cervical and kidney cell lines, likely due to altered membrane permeability resulting from drug protonation [9]. In aquatic models such as *Daphnia magna*, a decrease in water pH has been associated with increased acute toxicity of compounds such as

acetaminophen, enrofloxacin, and sulfathiazole, which may be attributed to changes in the proportion of unionized drug species [10].

Temperature is another critical physical factor influencing drug toxicity. Studies have shown that elevated water temperatures can intensify the acute toxicity of compounds such as acetaminophen, enrofloxacin, and chlortetracycline. This enhancement is likely due to changes in the toxicokinetics of these substances and their effects on the physiological responses of the test organism, *Daphnia magna* [10]. Similarly, high ambient temperatures have been found to exacerbate the toxic and lethal effects of psychostimulants such as methylenedioxymethamphetamine and methcathinone [11].

Exposure to UV-B light markedly enhanced the toxicity of sulfathiazole, likely due to photochemical modifications that induce oxidative stress. In contrast, enrofloxacin exhibited reduced acute toxicity under UV light, possibly as a result of photodegradation [10]. The cardiovascular drug atenolol showed no change in toxicity during photolysis. However, the toxicity of atorvastatin, bezafibrate, and metoprolol increased, which may be attributed to the formation of ketonized and hydroxylated photoproducts [12].

Furthermore, exposure of cells to electric fields can facilitate the entry of extracellular agents into the intracellular environment. This technique has been applied *in vivo* to enhance the uptake of chemotherapeutic drugs by tumor cells, resulting in significantly higher response rates compared to administration of the drug alone [13].

Since changing environmental conditions could affect exposure, concentration-response profile, and toxicity of drugs, such conditions should be identified and evaluated to better manage the health under changing physicochemical factors. Therefore, the present study aimed to measure the effect of certain physicochemical parameters on the toxicity of AMD in *Saccharomyces cerevisiae*.

Materials and Methods

Chemicals and Reagents

Amiodarone hydrochloride, Yeast Extract Peptone Dextrose (YPD) broth, agarose, and Dimethylsulfoxide (DMSO) were obtained from Sigma Aldrich (St. Quentin Fallavier, France).

Yeast Strain and Growth Condition

The *Saccharomyces cerevisiae* BY4741 wild-type strain (genotype: MATα, his3Δ1, leu2Δ0, met15Δ0, ura3Δ0) was provided by EUROSCARF (Germany). Cells were cultivated in YPD medium composed of 1% yeast extract, 2% peptone, and 2% dextrose.

Growth Rate Assessment

Yeast cells were cultured overnight in YPD medium (pH 7.43) at 30 °C until reaching the mid-exponential growth phase. The culture was then diluted with fresh YPD to achieve an optical density at 600 nm (OD_{600}) of approximately 0.18, corresponding to roughly 1.5×10^7 cells/mL. A stock solution of AMD at 20 mM was prepared in DMSO. Cells were treated with the appropriate volume of AMD and incubated at 30 °C with continuous shaking. Control cells received an equivalent volume of DMSO. Growth was assessed by measuring OD_{600} at time zero and after 5 h of incubation. Results were expressed as a percentage of growth relative to the untreated control, calculated using the following equation:

$$\text{Growth } \% = \frac{\text{X } \mathbf{OD}t - \text{X } \mathbf{OD}t0}{\text{C } \mathbf{OD}t - \text{C } \mathbf{OD}t0} x100$$

where X refers to cells treated with tested compounds and C refers to the control-untreated cells. The OD refers to optical density [3].

To determine the IC_{50} of AMD, yeast cells were exposed to a range of concentrations (0–160 µM) for 5 h. Growth profiles were monitored as previously described, and results were expressed as a percentage of growth relative to untreated control cells, using the aforementioned equation. The IC_{50} value was calculated by fitting the concentration–response data to a four-parameter logistic model using non-linear regression analysis in GraphPad Prism (GraphPad Software, La Jolla, CA) [2].

Treatment of Cells with Amiodarone at Different pH

Following a 12-h incubation, a 5 mL preculture was diluted in YPD medium adjusted to neutral (pH 7.43), basic (pH 10), or acidic (pH 4) conditions, until the optical density at 600 nm (OD_{600}) reached between 0.1 and 0.2. A stock solution of AMD at 20 mM was prepared in DMSO. Cells were then treated with appropriate volumes to achieve final AMD concentrations of 10, 20, 40, 80, and 160 µM, followed by incubation at 30 °C for 5 h.

Treatment of Cells with Amiodarone at Different Temperatures

At high temperature, the treatment was carried out according to the same protocol used at neutral pH. The samples containing different concentrations of AMD were incubated at 50 °C for 5 h.

At low temperature, after incubation, the preculture was placed in a refrigerator at T = - 20 °C for 30 min. Then, this preculture was diluted by neutral YPD to an optical density between 0.1 and 0.2. As before, with a stock solution of the same concentration, the cells were treated to obtain the same concentrations of previous AMD and were incubated under the same temperature and again for 5 h.

Treatment of Cells with Amiodarone under UV Exposure

After a 12-hour preculture incubation, the preculture was exposed to UV in the biological safety cabinet for 30 min. It was then diluted in a YPD medium at neutral pH until reaching an optical density (OD) between 0.1 and 0.2 at 600 nm.

The stock solution of AMD was prepared as before in DMSO. The cells were treated with the same final concentrations of AMD, and incubated at 30 °C for 5 h.

Treatment of cells with Amiodarone after electric shock

After a 12-hour preculture incubation, the preculture was shocked by an electrical current under tension 3 or 9 V. It was then diluted in YPD medium at neutral pH until reaching an OD between 0.1 and 0.2 at 600 nm.

The stock solution of AMD was prepared as before in DMSO. The cells were treated with the same final concentrations of AMD, and incubated at 30 °C for 5 h.

Measurement of the Quantity of CO2 Released

In sterile pots, 0.35 g of commercial yeast in the presence of 25 g of flour and 17 ml of distilled water were treated with the appropriate volume to obtain final [AMD] = 160, 320, 640 µM. They were mixed thoroughly to ensure a homogeneous distribution of AMD and to form a dough with a well-aligned surface. The samples were then incubated at 30 °C for 1 h 30 min.

Next, using a graduated ruler, the volume of CO_2 was estimated by measuring the height of the dough at 0 h and 1 h 30 min.

The data expressed in % of CO_2 were calculated after normalization to the control pots without AMD according to the following equation:

$$\%\ of\ CO2 = \frac{Height(X\ at\ t) - height(X\ at\ t=0h)}{Height(C\ at\ t) - height(C\ at\ t=0h)} \times 100$$

Where X refers to the mixture treated with AMD and C refers to the control mixture without AMD. The data were expressed as % CO_2 relative to that of the untreated control mixture using the equation above. Then, the half inhibitory concentration (IC_{50}) was calculated in the same way as above.

Statistical Analysis

Statistical analyses were performed using GraphPad Prism software. One-way ANOVA was applied, followed by either Bonferroni or Dunnett's post-hoc tests. A $p < 0.05$ was considered statistically significant.

Results

Dose-dependent Effect of Amiodarone on the Growth of BY4741 at Neutral pH

To assess AMD effect on the growth of *Saccharomyces cerevisiae* BY4741 strain, different doses were used in YPD medium at neutral pH (=7.43) for 5 h. Yeast growth was inhibited in a dose-dependent manner (Figure 1A) starting at 20 µM where the percentage of inhibition is 8% and reaches a maximum at 160 µM (63%) with an IC_{50} = 90.4 µM (Figure 1B).

Inhibition of Fermentation in Saccharomyces cerevisiae by Amiodarone

Yeast can use sugars to undergo aerobic respiration to produce water and CO_2 gas, or it can undergo fermentation in the absence of oxygen to produce ethanol and CO_2 gas [14]. We measured the percentage of CO_2 released by *Saccharomyces cerevisiae* after treatment with different concentrations of AMD in the dough. Then, the height of the latter was measured. A decrease in the percentage of this gas was observed after 1 h 30 min of treatment with 320 µM and 640 µM of AMD (percentages of CO2=78.67% and 31.67%, respectively) with an IC_{50} = 4931.1 µM (Figure 2A, B and C).

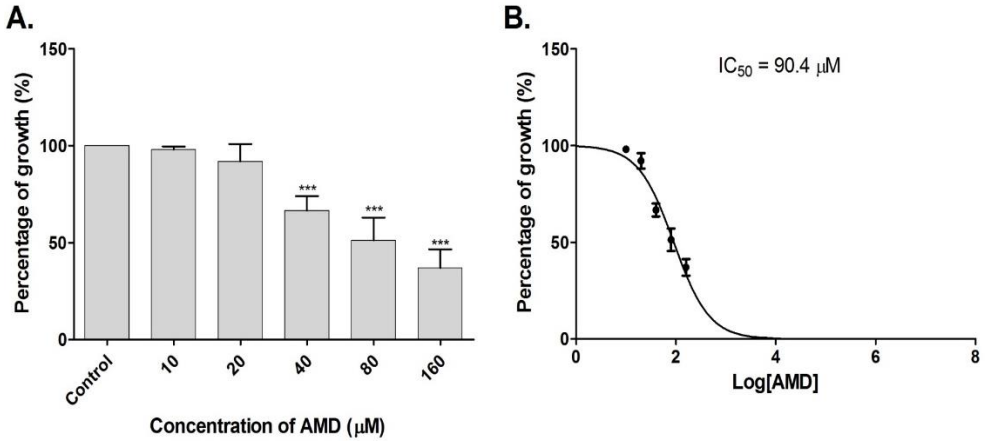

Figure 1. Dose-dependent toxic effect of AMD on the growth of wild-type yeast BY4741. Cells were treated with different AMD concentrations, and growth was assessed by optical density measurement at 5 h. (A) Results are expressed as % optical density relative to the untreated control cells and represent means ± SD from at least three independent experiments. (B) The IC_{50} was calculated using GraphPad Prism. (*) means a statistically significant result (p<0.05) compared with untreated cells.

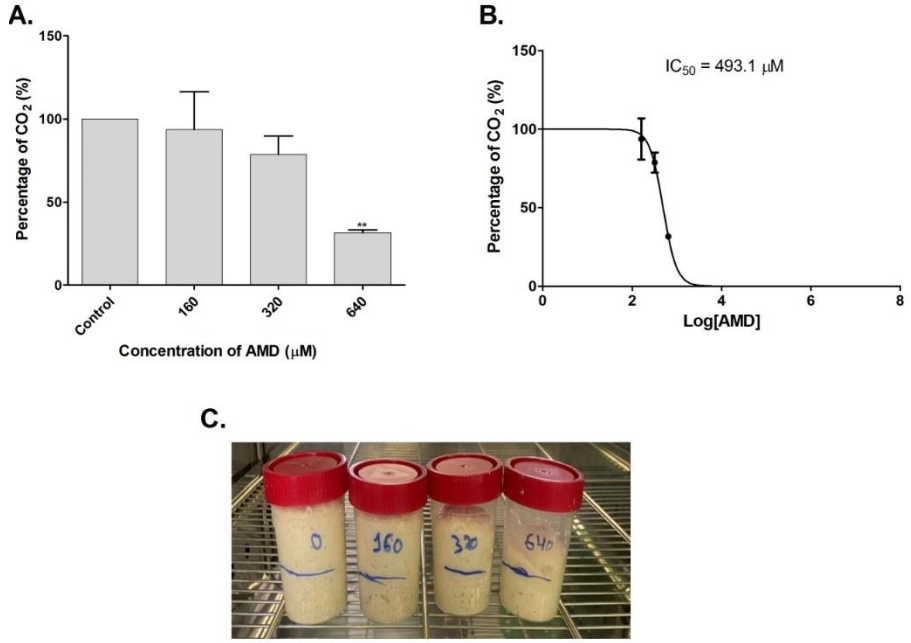

Figure 2. Effect of different doses of Amiodarone (AMD) on the percentage of CO_2 released in the dough. Cells mixed in the dough were treated with different AMD concentrations, and height was measured after 1 h 30 min. (A) Percentage of CO_2 released compared with untreated control cells, represented as means ± SD from at least three independent experiments. (B) the IC_{50} calculated by GraphPad Prism. (C) Dough observed under different conditions of treatment with AMD.

Slight Reduction of Amiodarone Toxicity by UV Exposure

It was revealed that cells exposed to UV for 30 min became more resistant to AMD, as evidenced by a decreased percentage of growth inhibition (Figure 3A) caused by this drug in normal conditions (Figure 1A). Consequently, the IC_{50} increased from 90.4 µM under normal conditions (Figure 1B) to 115 µM (Figure 3B).

Environmental pH-Dependent Variations in Amiodarone Toxicity

It was shown that acidic pH increased the toxicity of AMD in BY4741. For instance, 40 µM of AMD decreased the growth percentage of BY4741 by 33.6% compared to the control at neutral pH (Figure 1A). In contrast, the same concentration caused a 65% decrease at acidic pH (Figure 4A). Additionally, the IC_{50} at neutral pH was 90.4 µM (Figure 1B), while at acidic pH, it was 47.93 µM (Figure 4B). Conversely, basic pH greatly reduced the toxicity of AMD or the IC_{50} exceeding 160 µM (Figure 4C and D).

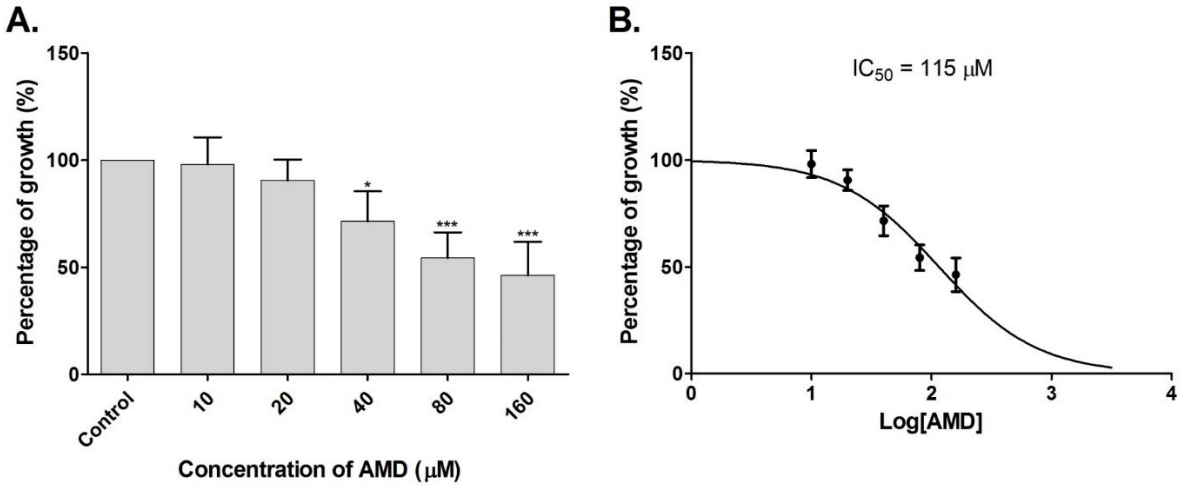

Figure 3. Dose-dependent toxic effect of AMD on growth of wild-type yeast BY4741 after incubation with UV. Cells were incubated 30 min with UV; then, treated with different AMD concentrations and growth was assessed by OD measurement at 5 h. (A) Results are expressed as % OD relative to the untreated control cells and represent means ± SD from at least three independent experiments. (B) IC_{50} was calculated using GraphPad prism. (*) means a statistically significant result (p<0.05) compared with untreated cells.

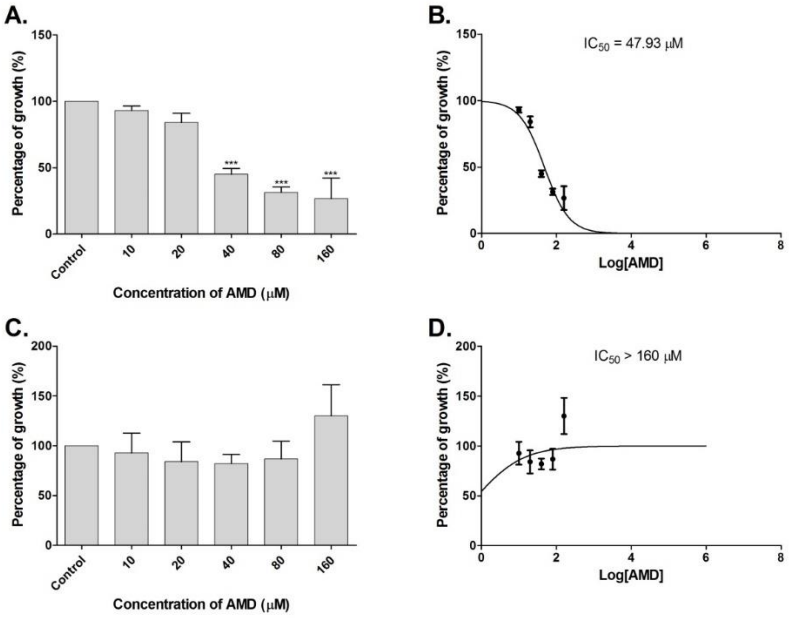

Figure 4. Dose-dependent toxic effect of AMD on the growth of wild-type yeast BY4741 at acidic or basic pH (A and C, respectively). Cells were treated with different AMD concentrations and growth was assessed by optical density measurement at 5 h. (A and C) Results are expressed as % optical density relative to the untreated control cells and represent means ± SD from at least three independent experiments. (B and D, corresponding to acidic or basic pH, respectively), IC_{50} was calculated using GraphPad Prism. (*) means a statistically significant result (p<0.05) compared with untreated cells.

Amiodarone Toxicity is affected by Electric Shock

The effect of electricity as one of the physical parameters on the toxicity of AMD was studied. For this purpose, the effect of two voltages (e.g., 3 and 9 V) on the toxicity was compared. It was revealed that 3 V voltage did not change the toxicity of AMD compared to standard conditions (data not shown). On the other hand, the 9 V voltage reduced the effect of AMD on *Saccharomyces cerevisiae* (Figure 5C and D). For example, 80 µM of AMD decreased the growth percentage of BY4741 by 48.75% compared to the control at the standard conditions (Figure 1A). On the other hand, the same concentration caused 35.67% decrease in the case of cells exposed to a voltage of 9 v (Figure 5A). Moreover, the IC_{50} was 90.4 µM (Figure 1B) in the first case and 469.2 µM in the second (Figure 5B).

High Temperature Sensitization of BY4741 to Amiodarone

In this study, the BY4741 was exposed to -20 °C and then was treated with AMD. The toxicity pattern (Figure 6A) is comparable to that of the standard conditions. Similarly, the IC_{50} (86.06 µM; Figure 6B) was almost equal to that observed in Figure 1B.

This was not the case for cells grown at 50 °C, where 80 µM of AMD, for example, caused 93.67% growth inhibition (Figure 6C), which was much greater than that observed at 30 °C (48.75%; Figure 1A). Similarly, the IC_{50} was 39.45 µM (Figure 6D), which was much lower than that obtained with AMD at an optimal temperature (Figure 1B). These results indicate that the temperature of 50 °C sensitizes the yeast to AMD.

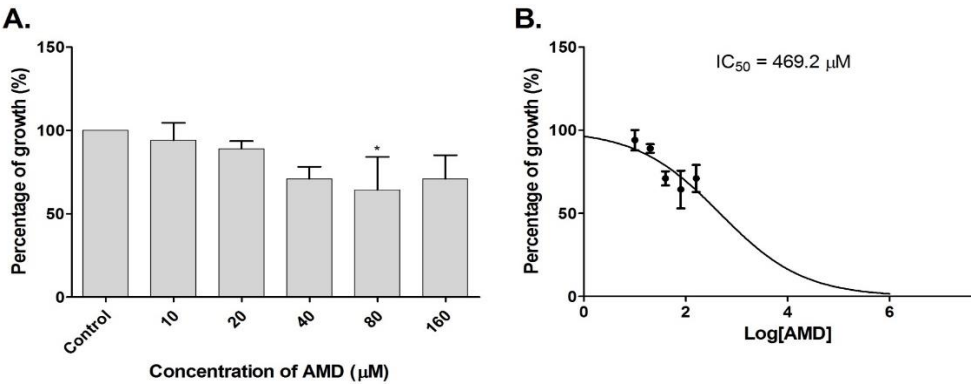

Figure 5. Dose-dependent toxic effect of AMD on the growth of wild-type yeast BY4741 after incubation under voltage 9 V. Cells were incubated 10 min under voltage 9 V; then, treated with different AMD concentrations and growth was assessed by optical density measurement at 5 h. (A) Results are expressed as % optical density relative to the untreated control cells and represent means ± SD from at least three independent experiments. (B) IC_{50} was calculated using GraphPad Prism. (*) means a statistically significant result (p<0.05) compared with untreated cells.

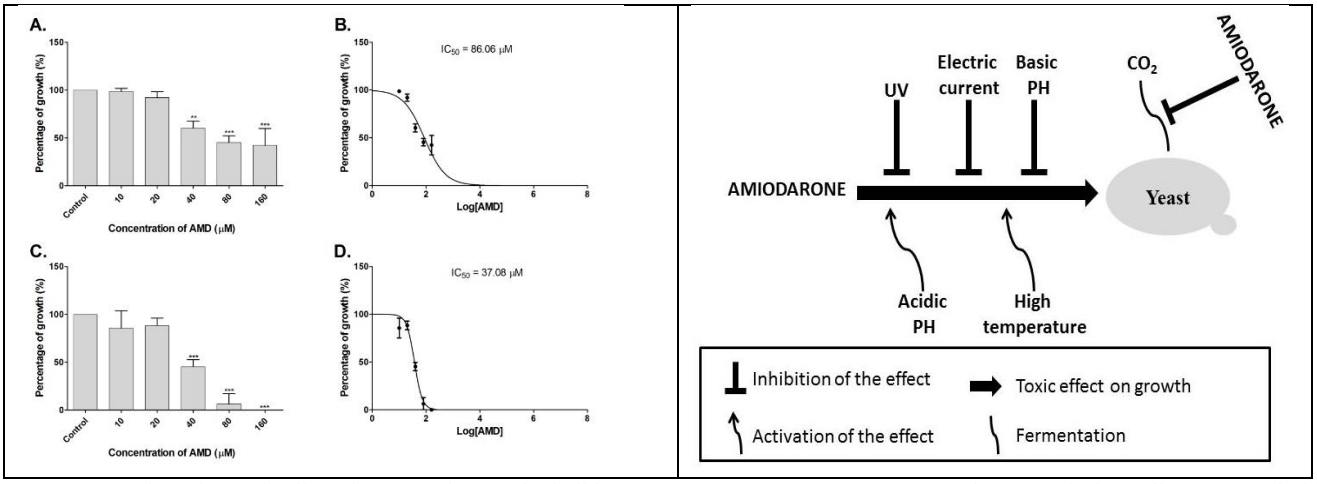

Figure 6. Dose-dependent toxic effect of AMD on the growth of wild-type yeast BY4741 at -20 or +50 °C (A and C, respectively). Cells were treated with different AMD concentrations, and growth was assessed by optical density measurement at 5 h under both temperature conditions of -20 or +50 °C. (A and C) Results are expressed as % optical density relative to the untreated control cells and represent means ± SD from at least three independent experiments. (B and D, corresponding to acidic and basic pH, respectively), IC_{50} was calculated using GraphPad Prism. (*) means a statistically significant result ($p<0.05$) compared with untreated cells.

Discussion

This study highlights the modulatory effects of environmental factors on AMD toxicity in yeast. Acidic pH enhanced AMD's inhibitory action, likely due to increased drug protonation and membrane permeability. Conversely, basic pH mitigated toxicity, suggesting reduced cellular uptake. The UV exposure appeared to induce resistance, potentially through DNA damage-induced mutations or drug photodegradation. Electrical stimulation at 9 V reduced AMD toxicity, possibly by altering membrane transporter activity. High temperature sensitized yeast cells, consistent with stress-induced vulnerability and altered metabolic responses.

The pH is recognized as a key chemical parameter in the cellular environment [15]. Alterations in acid-base balance can significantly impact various pharmacological properties of drugs, including their absorption in the gastrointestinal tract, distribution between plasma and cells, and excretion via urine [8]. In our study, we observed that at neutral pH, yeast growth was inhibited in a dose-dependent manner, consistent with previous findings on the toxicity of AMD and diclofenac in yeast [2, 3,16]. Furthermore, our results indicate that acidic pH enhances the toxicity of AMD, whereas basic pH mitigates this effect. These pH-dependent changes in drug activity are governed by physicochemical principles that influence the ratio of ionized to unionized species. Biological membranes preferentially allow the passage of lipophilic, unionized molecules while restricting the movement of hydrophilic, ionized forms [8]. Additionally, AMD has been shown to induce potassium (K^+) efflux at very low concentrations [17], and at higher concentrations, it promotes proton influx, leading to an increase in extracellular pH and a decrease in intracellular pH [17]. These pH shifts may contribute to the observed variations in AMD toxicity *in vitro*.

Previous studies have shown that sporulating cells of *Saccharomyces cerevisiae* are sensitive to UV irradiation [18]. In our investigation, however, we observed that yeast cells exposed to UV exhibited increased resistance to AMD. The UV irradiation is known to induce various forms of DNA damage, leading to specific mutations [19]. In a prior study, we demonstrated that AMD toxicity varied in mutated strains of *S. cerevisiae* compared to the wild-type strain [2,3], which could account for the increased resistance observed in our current findings. Additionally, UV exposure can degrade certain pharmaceutical compounds, such as diclofenac and sulfamethoxazole, potentially altering their toxicity profiles. This degradation may also contribute to the reduced toxicity of AMD following UV treatment [20].

Furthermore, our findings indicate that applying a 9 V electric current reduces the toxic effect of AMD on *Saccharomyces cerevisiae*. Previous research has shown that electric currents can influence the activity of certain membrane transporters [21]. In earlier work, we demonstrated that AMD toxicity is altered in yeast strains carrying mutations in genes encoding these transporters [2,3]. This suggests that the electric current may mitigate AMD toxicity by modulating the influx and efflux of the compound through its impact on transporter function.

Regarding the effect of temperature, our study shows that only high temperature (50 °C) sensitizes *Saccharomyces cerevisiae* to AMD. This finding aligns with previous research indicating that thermosensitization is most pronounced at extreme temperatures such as 0 °C and 15 °C, and less evident between 5–10 °C [22]. Additionally, other studies have demonstrated that hyperthermia can inhibit cancer cell proliferation by inducing G1 phase arrest and disrupting cell-cell interactions, while also enhancing

the efficacy of certain chemotherapeutic agents [23]. In *S. cerevisiae,* elevated temperatures are known to activate heat shock response genes [24]. Given that our previous work has shown AMD induces stress-dependent toxicity [2,3], the activation of stress pathways at higher temperatures may explain the increased sensitivity observed in this study which may explain the results obtained in this study.

We also demonstrated that AMD exerts toxic effects at the level of fermentation, as evidenced by a reduction in CO_2 production following treatment. The AMD is recognized as a steatotic compound [25] and fatty acids are known to induce toxicity in yeast by inhibiting CO_2 generation. This mechanism may underlie the observed toxicity of AMD in *Saccharomyces cerevisiae* [26].

Conclusions

It could be concluded that different physicochemical parameters can influence the toxicity of AMD. Among them are pH, UV, temperature, and electric current. This can still partly explain why different responses are observed among patients to certain idiosyncratic drugs, such as AMD.

Ethical Considerations

This is an *in vitro* study, so there are no ethical considerations.

Authors' Contributions

"Participated in research design: Houssein Al-Attrache, Sarah Al Gharib

Conducted experiments: Houssein Al-Attrache, Sarah Al Gharib, Zeina Alayan, Jana Ajam

Performed data analysis: Houssein Al-Attrache, Sarah Al Gharib

Wrote or contributed to the writing of the manuscript: Houssein Al-Attrache, Sarah Al Gharib

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Conflict of Interests

The author(s) declared no potential conflicts of interest concerning the research, authorship, and/or publication of this article.

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