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Effects of curcumin and nicorandil on nilotinib-induced QT interval prolongation in rats: A telemetry-based study

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Abstract: **Background**: Long QT syndrome (LQTS) is characterized by QT prolongation, ventricular arrhythmias and sudden death. Nilotinib (Nilo), a tyrosine kinase inhibitor used in chronic myeloid leukemia, prolongs QTc mainly through hERG (IKr) channel inhibition. Curcumin (Curc), often co-administered, modulates cardiac ion channels, whereas nicorandil (Nico) acts as a KATP channel opener. **Objectives**: This study evaluated the effects of Curc and Nico on Nilo-induced QTc prolongation. **Methods**: Male Sprague–Dawley rats implanted with radiotelemetry transmitters received 10 mg/kg nilotinib (selected as the minimal effective dose based on preliminary dose-finding studies at 10, 30 and 50 mg/kg), 100 mg/kg curcumin, or 10 mg/kg nicorandil, as previously described. Animals were allocated into seven groups: Control, Nilo, Curc, Nico, Nilo+Curc, Nilo+Nico and Nilo+Curc+Nico. ECG, biochemical and histopathological analyses were performed. Data were analyzed using one-way ANOVA followed by Tukey's post hoc test. **Results**: Nilotinib caused dose-dependent QTc prolongation, with 10 mg/kg as the minimal effective dose ($p<0.001$). Curcumin further exacerbated QTc prolongation, whereas nicorandil co-administration mitigated this effect. ($p<0.001$). Nilo also elevated TNF-α and TAS, which were attenuated in combination groups. **Conclusion**: Nilotinib-induced dose-dependent QTc prolongation was aggravated by curcumin, whereas nicorandil demonstrated a potential protective effect on drug-induced LQTS.

Keywords: Curcumin; KATP channels; Long QT syndrome; Nicorandil; Nilotinib

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INTRODUCTION

Sudden cardiac death (SCD) constitutes nearly half of all cardiovascular-related mortalities, with acute ventricular arrhythmias responsible for roughly 80% of cases (Singh *et al*., 2019). A central mechanism underlying these arrhythmias is QT interval prolongation, the electrophysiological hallmark of Long QT Syndrome (LQTS). LQTS reflects delayed ventricular repolarization and predisposes patients to torsades de pointes (TdP), syncope and arrhythmia-related sudden death (Shah *et al*., 2019). It may be congenital or acquired. The congenital form arises from mutations affecting cardiac ion channels, whereas the acquired form commonly results from drug-induced inhibition of the rapidly activating delayed rectifier potassium current (IKr) or electrolyte disturbances, leading to suppressed repolarization, prolonged ventricular action potential duration, and an increased risk of torsades de pointes (TdP) (Goldenberg and Moss, 2008). Given these mechanisms, the human ether-à-go-go-related gene (hERG) K^+ channels play a dual role as both therapeutic targets and key contributors to drug-induced cardiotoxicity. Recent findings emphasize that accurate QTc interval monitoring and individualized pharmacologic risk management play a crucial role in preventing arrhythmia-related adverse events in clinical settings (Tanveer *et al*., 2025). In clinical practice, QT intervals are corrected for heart rate using Bazett's formula ($QTc = QT/\sqrt{RR}$). QTc values exceeding 450 ms in men or 470 ms in women are considered prolonged, whereas QTc ≥500 ms markedly increases TdP risk. More than 90% of drug-induced TdP episodes occur at QTc values above 500 ms and each 10-ms increase confers an estimated 1.052-fold rise in risk (Webster *et al*., 2002). Although monitoring strategies have improved, there is still no established pharmacological therapy that directly reverses QT prolongation or prevents TdP in acquired or drug-induced LQTS (Tan *et al*., 2024). Current management largely relies on discontinuation of the offending drug and correction of electrolyte imbalances rather than mechanism-based interventions. This continuing therapeutic gap highlights the urgent need for novel cardioprotective compounds that can safely counteract drug-induced repolarization disturbances without compromising therapeutic efficacy. Research continues to develop drugs that reverse QT prolongation and lower arrhythmia risk. Nilotinib, a second-generation tyrosine kinase inhibitor (TKI) used in imatinib-resistant chronic myeloid leukemia, prolongs the QT interval primarily through potent hERG channel inhibition. Clinical data report a ~0.3% incidence of SCD among patients receiving nilotinib therapy (Fradley and Moslehi, 2015). In cancer patients, particularly those with CML, polypharmacy and comorbidities exacerbate the challenge of managing side effects, as treatment discontinuation or alternative therapeutic options may be limited (Chan *et al*., 2024). Recent induced pluripotent stem cell–derived (iPSC-

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derived) cardiomyocytes studies demonstrate that nilotinib impairs electromechanical coupling, prolongs action potential duration and disrupts calcium and mitochondrial homeostasis, further supporting its proarrhythmic potential. These findings highlight the need for effective preventive strategies against TKI-induced arrhythmogenic risk. Nilotinib has been reported to exhibit both pro-oxidant and antioxidant properties; which may contribute to its dual effects on different organs (Izumi-Nakaseko *et al*., 2025; Zhou *et al*., 2013; Ateyya *et al*., 2017). However, it has also been shown that nilotinib increases reactive oxygen species (ROS) production by 1.4-fold at a concentration of 3 μM and by 4.6-fold at 10 μM, potentially contributing to apoptosis through oxidative stress-related pathways (Doherty *et al*., 2013). Curcumin, a polyphenolic compound from Curcuma longa, exhibits antioxidant, anti-inflammatory and antitumor activities but may inhibit hERG channels and prolong the QT interval (Gupta *et al*., 2012) A recent study demonstrated that curcumin significantly prolonged the action potential duration in iPSC-derived cardiomyocytes carrying the KCNE1-D85N variant (Martinez *et al*., 2023), while another showed that curcumin attenuated doxorubicin-induced QT prolongation and oxidative stress by modulating NF-κB and Apelin signaling (Akca *et al*., 2025). Nicorandil is a dual-acting agent approved for the treatment of angina pectoris and heart failure due to its potent coronary vasodilatory effects and its ability to activate ATP-sensitive potassium (K_ATP) channels. Nicorandil has been shown to prevent QT prolongation and myocardial damage in rat models of drug-induced cardiotoxicity, likely via mitochondrial KATP activation and oxidative stress suppression. It also exhibits antiarrhythmic effects by shortening QT intervals, stabilizing repolarization and reducing ventricular arrhythmias, as demonstrated in hypokalemia-induced LQTS models. However, some studies report no significant effect on QT interval, highlighting the variability of its response (Huang, 2017; Akturk *et al*., 2023).

Despite extensive characterization of TKI-induced cardiotoxicity, few studies have explored pharmacological strategies to mitigate nilotinib-related QTc prolongation. Preclinical models are therefore essential for identifying safe interventions, especially given the ethical limitations restricting clinical evaluation of drug-induced QT prolongation. However, a critical knowledge gap remains: no study to date has systematically evaluated whether agents possessing electrophysiological modulatory properties can effectively attenuate or reverse nilotinib-induced QTc prolongation *in-vivo*. Existing work has examined curcumin and nicorandil in unrelated cardiotoxicity or LQTS models, but their individual or combined effects specifically in a telemetry-based model of nilotinib-induced QTc prolongation have not been investigated. Furthermore, the contribution of KATP channel activation to potential antiarrhythmic protection in this context remains unclear, leaving a significant gap in mechanism-based therapeutic strategies.

The role of K_ATP channels in mediating cardioprotection and antiarrhythmic effects remains incompletely understood. As in the case of nilotinib therapy for CML, effective and safe pharmacological agents are needed to manage LQTS without compromising anticancer efficacy. Accordingly, research continues on the efficacy of K-ATP channel openers such as nicorandil, cromakalim and pinacidil. Nicorandil, through its dual mechanism of nitrate donation and K_ATP channel opening, exhibits cardioprotective and electrophysiological effects and has been proposed as a potential therapeutic agent for LQTS. Experimental studies have shown that nicorandil can shorten QT intervals and reverse repolarization abnormalities in acquired LQTS models; however, conflicting results regarding its antiarrhythmic efficacy necessitate further investigation (Akturk *et al*., 2023).

Given the urgent need for safe pharmacological agents capable of mitigating drug-induced QTc prolongation without compromising anticancer efficacy, this study investigated the effects of curcumin and nicorandil—agents with distinct antioxidant and electrophysiological properties—on nilotinib-induced QTc prolongation in rats. Curcumin, a potent antioxidant and anti-inflammatory polyphenol and nicorandil, a K_ATP channel opener with well-established cardioprotective and antiarrhythmic actions, were selected for their complementary mechanisms in counteracting electrophysiological disturbances and oxidative injury. Electrocardiographic evaluations were integrated with biochemical and histopathological analyses to determine whether these agents, individually or in combination, could prevent or ameliorate nilotinib-induced QTc prolongation. The findings of this study are expected to provide mechanistic insight and experimental evidence supporting the development of safer adjunctive strategies for patients requiring long-term tyrosine kinase inhibitor therapy.

MATERIALS AND METHODS

Animals

Seventy-four adult male Sprague–Dawley rats (6–8 wks, 200–250g) were housed under controlled temperature (20–22°C), humidity and a 12-h light/dark cycle with ad libitum access to food and water; after a 1-wk acclimation, rats were individually housed during post-surgical recovery and subsequently group-housed (four per cage)

Surgical preparation and radiotelemetrytransmitter implantation

Surgical procedures were performed under ketamine (80 mg/kg, i.p.) and xylazine (8 mg/kg, i.p.) anesthesia. A telemetry transmitter (Model C50PXT or F40; DSI, St.

Paul, MN, USA) was implanted into the abdominal cavity via a 5–6 cm midline incision. Biopotential leads were tunneled subcutaneously and positioned at the forelimb level to facilitate standard Lead II electrocardiography (ECG) acquisition. These transmitter models were selected for their validated high-fidelity ECG acquisition in conscious, freely moving animals (Kramer *et al*., 2013; Wallis *et al*., 2018; Authier *et al*., 2020) Electrodes were positioned subcutaneously at the forelimb level to obtain a standard lead II ECG configuration. The transmitter body was secured to the abdominal wall using non-absorbable polypropylene sutures to minimize motion artifacts. To prevent perioperative hypothermia and corneal dryness, a heating pad and Carbomer eye gel (Viscotears) were applied, respectively. Preoperatively, rats received a single dose of ciprofloxacin (90 mg/kg, sc) for infection prophylaxis. Postoperative analgesia was maintained with intraperitoneal tramadol (50 mg/kg on day 0; 25 mg/kg on days 1–2), following established postoperative care protocols in telemetry studies. Vitamin C (1 g/L) was added to drinking water to support recovery and minimize oxidative stress. Animals were housed individually and monitored daily until full recovery, defined by restoration of body weight and spontaneous mobility.

ECG recording and data analysis

Continuous ECG recordings were obtained from conscious, freely moving rats using a radio telemetry system (DSI, St. Paul, MN, USA) and analyzed with Ponemah® Software (v630). This non-invasive telemetry approach was chosen to allow real-time cardiac monitoring without anesthesia-induced interference on heart rate and QT interval. Data were acquired at a sampling rate of 1000 Hz and analyzed for heart rate (HR), PR interval, QRS duration, QT interval and Bazett-corrected QT (QTc = QT/√RR). Recordings were taken every 15 minutes for 8 hours following drug administration, always at the same time of day to avoid circadian variations. This telemetry-based approach allowed real-time, anesthesia-free monitoring under minimally stressful conditions. Before each experiment, the telemetry system was calibrated according to the manufacturer's instructions and QT intervals detected by Ponemah® software were manually confirmed in a subset of recordings (Nyakas *et al*., 1990; Dogan *et al*., 2000; Kramer and Kinter, 2003).

Drugs and chemicals

Nilotinib (Nilotinib, Sigma-Aldrich, St. Louis, USA), curcumin (*Curcuma longa*, Sigma-Aldrich, MO, USA), nicorandil (Nicorandil, Sigma-Aldrich, MO, USA), Vitamin C (Fluka GmbH Buchs, Switzerland) ketamine (Alfamine 10%, Alfasan International B.V., Netherlands), xylazine (Xylazinbio 2%, Bioveta PLC, Czech Republic), tramadol (Tramadol HCl, Sigma Aldrich, USA), Cipro (Ciprofloxacin, Biofarma, Turkey) and Carbomer eye gel (Viscotears, Novartis, Switzerland) were used. Biochemical analyses were performed using ELISA kits (YL Biotech Co. Ltd., Shanghai, China), following the manufacturer's instructions. All drugs were freshly prepared on the day of use and suspended in 5% DMSO + saline to ensure consistent oral delivery and stability

Experimental protocols

The study consisted of two phases: a preliminary dose-determination phase and a main experimental phase.

Preliminary study (dose determination and timing assessment)

A total of 24 male Sprague-Dawley rats (6-8 weeks old, 200-250 g) were used.

Determination of QT-prolonging dose and ECG onset time of nilotinib.

Rats were divided into three groups (n=4 per group) and administered nilotinib at doses of 10, 30, or 50 mg/kg p.o. to determine the minimum effective QTc-prolonging dose. The onset times of ECG changes were also evaluated following single oral administrations of nilotinib (10 mg/kg, p.o.), curcumin (100 mg/kg, po) and nicorandil (10 mg/kg, p.o.). The selected doses and administration times were based on previous literature and preliminary dose-response assessments: nilotinib 10 mg/kg was the minimum effective QTc-prolonging dose, curcumin 100 mg/kg provided optimal systemic antioxidant/anti-inflammatory effects and nicorandil 10 mg/kg was effective for K_ATP-mediated cardioprotection. Timing before ECG recording (3 hrs for nilotinib, 60 mins for curcumin, 50 mins for nicorandil) was chosen based on preclinical pharmacokinetic data and reported onset/ Tmax values in rodents. Nilotinib reaches maximal plasma concentrations in rodents within ~0.5–4 hrs depending on dose and formulation; curcumin shows a rapid absorption in rats with reported T_{max} values around 40–60 mins after oral dosing; and nicorandil is rapidly absorbed in rodents with reported T_{max} values near 0.4–0.6 hrs (≈24–36 mins), supporting an ECG timing of ~50 mins in our model. Where direct ECG onset-of-action data were absent, timing was confirmed by pilot observations (Pisano *et al*., 2010; Sahin *et al*., 2023; Xia *et al*., 2012; Dutra *et al*., 2013; Frydman *et al*., 1989)

Main experimental groups

Fifty-six male Sprague-Dawley rats were divided into seven groups (n=8/ group):

1.Control: 5% DMSO + saline p.o.
2.Nilo: Nilotinib 10 mg/kg in 5% DMSO + saline po
3.Nico: Nicorandil 10 mg/kg in 5% DMSO + saline po
4.Curc: Curcumin 100 mg/kg in 5% DMSO + saline po
5.Nilo+Curc: Nilotinib 10 mg/kg + Curcumin 100 mg/kg in 5% DMSO + saline po
6.Nilo+Nico: Nilotinib 10 mg/kg + Nicorandil 10 mg/kg in 5% DMSO + saline po
7.Nilo+Curc+Nico: Nilotinib 10mg/kg+Curcumin 100mg/kg+ Nicorandil 10mg/kg in 5% DMSO + saline po

Nilotinib was administered orally 3 hrs, curcumin 60 mins and nicorandil 50 mins before ECG recording (p.o.)

Biochemical analyses and histological examination

Cardiac tissue was assessed for histomorphology, oxidative/antioxidative status and inflammatory cytokines. The heart was bisected; the left half (septum and left ventricle) was fixed in 10% formalin for histology, while the right half was washed with PBS and stored at –80°C for biochemical analysis. Samples were homogenized (IKA-T25 Easy Clean Digital) and centrifuged at 13,000 rpm for 15 minutes. Homogenates were analyzed for TAS (total antioxidant capacity), TOS (total oxidant capacity), TNF-α and IL-6 using ELISA kits (YL Biotech, Shanghai, China) and absorbance was measured with a microplate reader (BioTek ELX 800, USA)

Statistical analysis

Data were analyzed using SPSS 15.0 (SPSS Inc., Chicago, IL, USA). Normality was assessed prior to hypothesis testing. Comparisons between the three dose groups in the preliminary phase were performed using one-way ANOVA. For the main experimental groups, normally distributed variables (TNF-α, IL-6 and TAS) were analyzed using one-way ANOVA followed by Tukey's post-hoc test for multiple comparisons. Non-normally distributed data (TOS) were analyzed using the Kruskal-Wallis test. Data are presented as mean ± standard error (SE). A p-value of <0.05 was considered statistically significant.

RESULTS

Dose-dependent effect of nilotinib on QTc interval

Nilotinib was administered orally at doses of 10, 30 and 50 mg/kg (n=4) based on literature and, QTc values were compared. Statistical differences were observed depending on the dose ($p=0.03$, $p<0.001$ and $p<0.001$, respectively). A dose-dependent prolongation of the QTc interval was observed when the nilotinib dose was increased from 10 to 50 mg/kg. The 10 mg/kg dose was chosen for subsequent experiments because it was the minimum dose that caused a statistically significant increase in QTc ($p=0.03$). The lowest effective dose of nilotinib was chosen to ensure sufficient sensitivity to observe the small changes resulting from the co-administration of curcumin and nicorandil. At this dose, QTc prolongation began at the 3rd hour, corresponding with Tmax and no mortality was observed (Table 1). Nilotinib has a clearly dose-dependent QTc prolongation effect, whereas Curcumin and Nicorandil were evaluated as single doses and their dose-dependent effects were not studied.

Electrocardiographic findings

Baseline electrocardiographic parameters

Baseline parameters (HR, PR, QRS, QT, QTc) showed no significant differences between preliminary and experimental groups ($p> 0.05$), indicating homogeneity across groups (Table 2).

Baseline parameters of the experimental groups

Baseline ECG parameters did not differ significantly between groups ($p> 0.05$) (Table2).

Effects of the agents on selected electrocardiographic parameters

The effects of nilotinib (10 mg/kg), curcumin (100 mg/kg) and nicorandil (10 mg/kg), all administered orally, on HR, PR interval, QRS duration, QT and QTc were monitored over an 8-hour period.

Effect of nilotinib on ECG parameters

When the effects of Nilotinib were evaluated in comparison to baseline values, the results were as follows: HR: $365.99 \pm 3.50 \rightarrow 292.57 \pm 3.29$ ($p<0.001$), PR: $58.32 \pm 0.54 \rightarrow 57.86 \pm 0.48$ ($p>0.05$), QRS: $17.16 \pm 0.16 \rightarrow 19.54 \pm 0.40$ ($p<0.001$), QT: $87.58 \pm 0.73 \rightarrow 107.48 \pm 0.44$ ($p<0.001$), QTc: $216.65 \pm 0.97 \rightarrow 245.80 \pm 1.05$ ($p<0.001$).

A significant QTc prolongation was observed at the 3rd hour post-administration, consistent with literature indicating onset around this time (Zhou *et al*., 2013).

Effect of curcumin on ECG parameters

Curcumin administration resulted in changes beginning at the 60th minute post-administration, consistent with previous reports. The comparison to baseline yielded the following: HR: $365.99 \pm 3.50 \rightarrow 263.32 \pm 1.54$ ($p<0.001$), PR: $58.32 \pm 0.54 \rightarrow 67.27 \pm 0.81$ ($p<0.001$), QRS: $17.16 \pm 0.16 \rightarrow 16.04 \pm 0.38$ ($p>0.05$), QT: $87.58 \pm 0.73 \rightarrow 118.94 \pm 0.54$ ($p<0.001$), QTc: $216.65 \pm 0.97 \rightarrow 249.78 \pm 0.63$ ($p<0.001$).

QTc prolongation was significant at 60 minutes ($p<0.001$), consistent with prior rat studies using 100 mg/kg oral curcumin (Horinaka *et al*., 2001).

Effect of nicorandil on ECG parameters

Nicorandil did not cause significant changes in ECG parameters, consistent with previous reports (Horinaka *et al*., 2001; Lu *et al*., 1999). The following values were obtained: HR: $365.99 \pm 3.50 \rightarrow 360.57 \pm 3.66$ ($p>0.05$), PR: $58.32 \pm 0.54 \rightarrow 50.81 \pm 0.54$ ($p>0.05$), QRS: $17.16 \pm 0.16 \rightarrow 17.30 \pm 0.33$ ($p>0.05$), QT: $87.58 \pm 0.73 \rightarrow 88.50 \pm 0.84$ ($p>0.05$), QTc: $216.65 \pm 0.97 \rightarrow 217.20 \pm 1.23$ ($p>0.05$).

These findings confirm that Nicorandil (10 mg/kg, p.o.) did not alter electrocardiographic parameters significantly ($p>0.05$) (Table 3).

Table 1: Dose of nilotinib that prolongs the QT interval

Groups	Baseline measurement (ms)	3 h measurement (ms)	*p*-value	Statistical test
Nilo10	223.17 ± 0.99	227.69 ± 0.97	0.03	
Nilo30	223.22 ± 1.09	236.51 ± 0.83	*p*<0.001	Paired sample
Nilo50	218.16 ± 0.88	242.04 ± 1.76	*p*<0.001	t-Test

Table 2: Baseline electrocardiographic parameters of the preliminary study groups

Groups	HR (beats/min)	PR (ms)	QRS (ms)	QT (ms)	QTc (ms)
Preliminary groups					
Nilo	351.13±1.73	47.38±0.46	17.00±0.19	92.38±0.71	211.15±3.79
Curc	350.29±1.78	47.13±0.29	16.88±0.12	91.63±0.56	213.63±2.01
Nico	352.11±2.64	47.38±0.37	17.06±0.06	92.38±0.71	212.88±4.02
Experimental groups					
Control	352.84 ± 1.16	47.60 ± 0.4	17.00 ± 0.18	92.24 ± 0.61	213.52 ± 2.79
Nilo	351.13 ± 1.73	47.38 ± 0.46	17.00 ± 0.19	92.38 ± 0.71	211.15 ± 3.79
Nilo+Curc	351.50 ± 0.73	47.00 ± 0.38	16.76 ± 0.31	93.00 ± 0.89	210.38 ± 1.88
Nilo+Nico	352.50 ± 1.40	47.75 ± 0.31	17.00 ± 0.18	92.50 ± 0.60	211.40 ± 3.10
Nilo+Curc+Nico	351.75 ± 1.63	47.00 ± 0.37	16.94 ± 0.19	91.63 ± 0.50	212.02 ± 3.02

HR: Heart rate, Nilo: Nilotinib, Curc: Curcumin, Nico: Nicorandil.

Table 3: Effects of the agents used on QTc interval

Groups	Baseline measurement (ms)	Final measurement (ms)	*p*-values
Nilo 10mg/kg	211.145 ± 3.79	242.625 ± 1.05	*p*<0.001
Curc 100mg/kg	213.625 ± 2.00	248.375 ± 1.14	*p*<0.001
Nico 10 mg/kg	212.875 ± 4.02	208.512 ± 2.28	*p*=0.299

Nilo: Nilotinib, Curc: Curcumin, Nico: Nicorandil.

Comparison of parameters between groups

QTc interval

QTc interval values were: Control 216.65 ± 0.97 ms, Nilo 245.80 ± 1.05 ms, Curc 249.78 ± 0.63 ms, Nico 217.20 ± 1.23 ms, Nilo+Curc 277.85 ± 1.24 ms, Nilo+Nico 231.09 ± 0.65 ms and Nilo+Curc+Nico 239.43 ± 0.77 ms. QTc was significantly prolonged in all treatment groups compared with Control, except Nico (p<0.001) and no difference was detected between Nico and Control (p>0.05). Relative to Nilo, QTc was further increased in Nilo+Curc, but decreased in Nilo+Nico (p<0.001). The increase in Nilo+Curc was also significant versus Curc alone, whereas co-administration of Nico significantly reduced QTc compared with Nilo+Curc (p<0.001) (Fig. 1).

Significant QTc interval prolongation was observed in the Nilo + Curc group, and this effect was likely mediated by inhibition of the hERG K^+ channel (Fig. 2B). Additionally, T-wave negativity, which is expressed as a component of LQTS, was observed (Fig. 2C and 2D).

QT interval

QT intervals (ms) were: Control 87.58 ± 0.73, Nilo 107.48 ± 0.44, Curc 118.94 ± 0.54, Nico 88.50 ± 0.84, Nilo + Curc 140.22 ± 0.93, Nilo + Nico 99.40 ± 0.58 and Nilo + Curc + Nico 105.86 ± 0.65. All groups except Nico differed significantly from Control (p<0.001). No difference was found between Nico and Control (p> 0.05). Compared to Nilo, QTc was significantly prolonged in Nilo + Curc (p <0.001) and reduced in Nilo + Nico (p<0.001), with no difference between Nilo and Nilo + Curc + Nico (p>0.05). Nilo + Curc also showed significant prolongation versus Curc alone (p<0.001) (Fig. 3A).

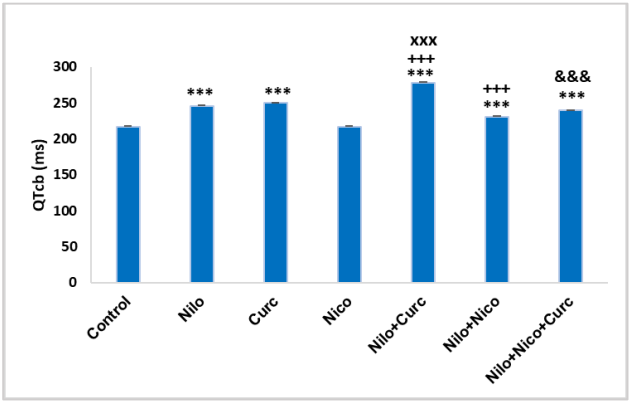

Fig. 1: Comparison of adjusted QT interval (QTc) between groups (ms). ***p<0.001; vs. Control, +++p<0.001; vs. Nilo, xxxp<0.001; vs. Curc, &&&p<0.001; vs. Nilo + Curc. Nilo: Nilotinib, Curc: Curcumin, Nico: Nicorandil.

QRS interval

QRS values were: Control 17.16 ± 0.16 ms, Nilo 19.54 ± 0.40 ms, Curc 16.04 ± 0.38 ms, Nico 17.30 ± 0.33 ms, Nilo+Curc 18.55 ± 0.20 ms, Nilo+Nico 18.65 ± 0.26 ms and Nilo+Curc+Nico 18.50 ± 0.17 ms. QRS was significantly prolonged in the Nilo and combination groups compared with Control (p<0.001), while Curc and Nico did

not differ from Control (p>0.05). Compared with Nilo, both Curc and Nico significantly reduced QRS duration (p<0.001). No significant differences were detected among the Nilo+Curc, Nilo+Nico and Nilo+Curc+Nico groups (p>0.05) (Fig. 3B).

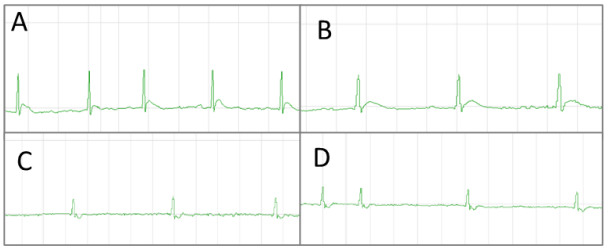

Fig. 2: Representative ECG tracings: (A) normal QT interval; (B) QT prolongation; (C–D) T-wave inversion.

Heart rate (HR)

Heart rates (bpm) were: Control 365.99 ± 3.50, Nilo 292.57 ± 3.29, Curc 263.32 ± 1.54, Nico 360.57 ± 3.66, Nilo + Curc 234.96 ± 1.55, Nilo + Nico 323.25 ± 2.15 and Nilo + Curc + Nico 305.43 ± 2.09. Significant reductions versus Control were observed in all groups except Nico (p<0.001), with no difference between Nico and Control (p>0.05). Compared to Nilo, Curc and Nilo + Curc + Nico showed no significant difference (p>0.05). Significant differences were found in Nico, Nilo + Curc and Nilo + Nico groups (p<0.001) (Fig. 3C).

PR interval

PR intervals (ms) were: Control 58.32 ± 0.54, Nilo 57.86 ± 0.48, Curc 67.27 ± 0.81, Nico 50.81 ± 0.54, Nilo + Curc 68.24 ± 0.58, Nilo + Nico 54.91 ± 0.67 and Nilo + Curc + Nico 56.90 ± 0.52. Significant differences were observed between control and Curc, Nico and Nilo + Curc groups (p<0.001), while no differences were found among Nilo, Nilo + Nico and Nilo + Curc + Nico groups (p>0.05). Curc, Nico and Nilo + Curc groups also differed significantly (p<0.001) (Fig. 3D).

ECG parameters showed that QT interval was significantly prolonged in all treatment groups except Nicorandil. QRS duration increased significantly in the Nilotinib and combination groups. Heart rate significantly decreased in all groups except the Control and Nicorandil groups. Curcumin prolonged the PR interval, while Nicorandil partially reversed this effect.

Biochemical findings

Biochemical analysis of heart tissue homogenates revealed group-specific alterations in TNF-α, IL-6, TOS and TAS levels (Fig.4A-D). TNF-α: Nilotinib significantly increased TNF-α levels (p<0.05), with a more pronounced rise in the Nilo + Nico group (p<0.001 vs. Control). Co-administration with curcumin attenuated this increase (p<0.05 vs. Nilo), whereas the Nilo + Nico group showed higher TNF-α than the Nilo + Curc group (p<0.001). TNF-α was markedly elevated by Nilotinib and further by Nicorandil co-treatment but was reduced by Curcumin (Fig. 4A). IL-6 & TOS: No significant differences were detected among groups (p>0.05) (Figs.4B and 4C). TAS levels significantly increased in the Nilo group (p<0.001 vs. Control) but decreased with both curcumin (p<0.001) and nicorandil (p< 0.01) co-treatment. TAS was lower in the Nilo + Curc group compared to the Nilo + Curc + Nico group (p<0.05). Thus, Nilotinib elevated TAS, which was mitigated by Curcumin and Nicorandil (Fig. 4D).

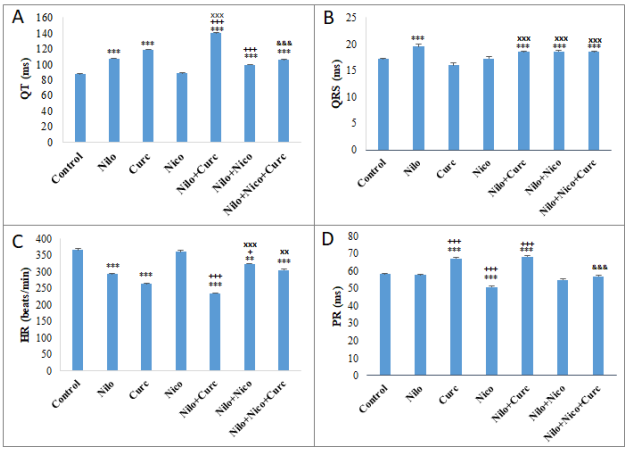

Fig 3: Comparison of ECG parameters across experimental groups (A) QT interval (ms); (B) QRS interval (ms); (C) HR (beats/min); (D) PR interval (ms). (Nilo: Nilotinib, Curc: Curcumin, Nico: Nicorandil, HR: Heart Rate). (***p<0.001; vs. Control, +++p<0.001; vs. Nilo, xxxp<0.001; vs. Curc, &&&p<0.001; vs. Nilo + Curc).

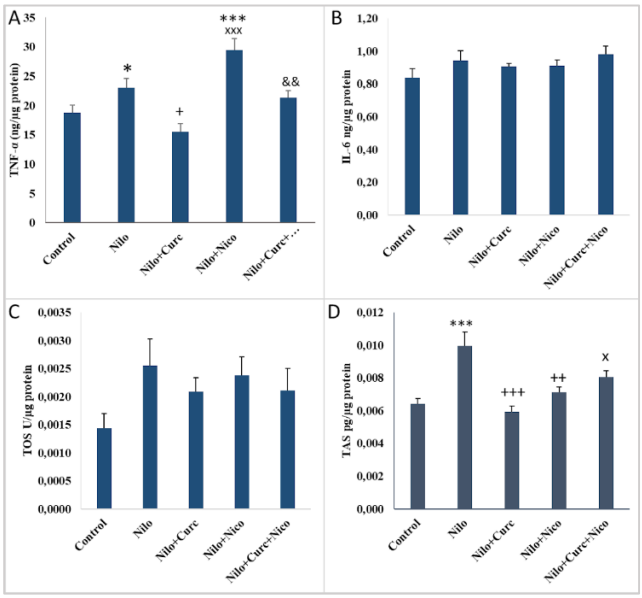

Fig. 4: Comparative cardiac biochemical analysis across experimental groups (A) TNF-α (ng/µg protein) levels; (B) IL-6 (ng/µg protein) levels; (C) TOS (U/µg protein) levels; (D) TAS (pg/ µg protein levels. (Nilo: Nilotinib, Curc: Curcumin, Nico: Nicorandil) (*p<0.05; ***p<0.001; vs. Control, ^{x}p<0.05; ^{xxx}p<0.001; vs. Nilo+Curc, $^{+}$p<0.05; $^{++}$p<0.01; $^{+++}$p<0.001; vs. Nilo, $^{\&\&}$p<0.01; vs. Nilo+Nico).

Histological findings

Histopathological evaluation of heart tissue. Cardiac sections from all groups showed preserved myocardial architecture with centrally located nuclei and normal cytoplasm. No significant differences were noted between treated groups. There was no evidence of vacuolization, necrosis, vasodilation, or inflammatory infiltration, indicating structurally intact myocardium and supporting the presence of mild, reversible biochemical alterations (Fig. 5).

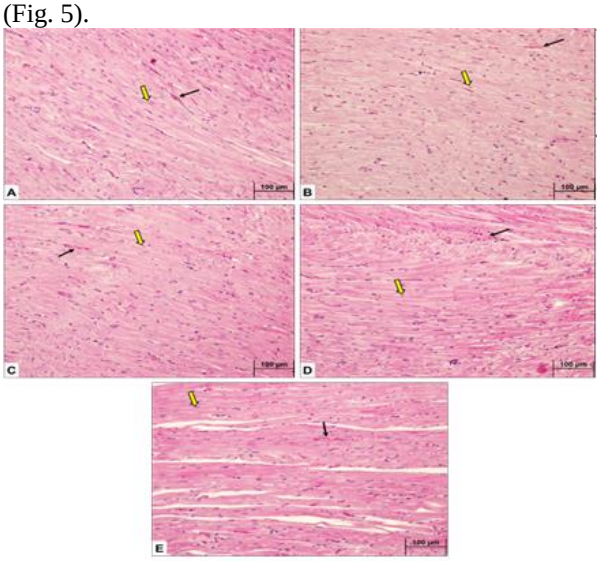

Fig. 5: Histological evaluation of groups. (A) Control; (B) Nilo; (C) Nilo+Curc; (D) Nilo+Nico; (E) Nilo +Curc+Nico. Black arrow: vascular structure; Yellow arrow: cardiomyocyte

DISCUSSION

Nilotinib, a second-generation TKI used as standard therapy for imatinib-resistant chronic myeloid leukemia (CML), is increasingly associated with off-target cardiovascular effects, including QT interval prolongation, arrhythmias, and heart failure. Among these effects, QT prolongation is of particular concern, as inhibition of hERG potassium channels disrupts myocardial repolarization and increases the risk of life-threatening arrhythmias such as TdP (Yang *et al*., 2018).

In the present study, a LQTS model was successfully established using a single oral dose of 10 mg/kg nilotinib. This dose was identified as the minimal effective dose capable of inducing significant QTc prolongation, corroborating limited preclinical data (Serrya *et al*., 2021; Samaha *et al*., 2019; Abdelgalil *et al*., 2019). Notably, preclinical data on the QT-prolonging dose of nilotinib in rat models remain very limited; therefore, valuable insights into dose selection and electrophysiological effects in this species are provided. A clear dose-dependent QTc prolongation was observed, likely reflects direct inhibition of cardiac potassium channels and increased susceptibility to ventricular arrhythmias. These results are in line with clinical data that led to the FDA's black box warning for nilotinib-associated QT prolongation (le Coutre *et al*., 2012). Given the acute male-only model, lack of chronic exposure and absence of arrhythmic or survival endpoints, translational applicability is limited. Continuous telemetry provided high-resolution ECG data, yet these findings primarily reflect early electrophysiological changes rather than definitive proarrhythmic risk (Savenkov *et al*., 1988; Kramer *et al*., 1993).

Additionally, significant increases in TNF-α levels were observed in cardiac tissue of the nilotinib-administered groups. As reported, an increase in TNF-α, IL-6 and IL-1β may enhance ROS production and contribute to QT prolongation through the ceramide/S1P pathway (Savenkov *et al*., 1988). Increases in TNF-α levels following nilotinib exposure were consistent with prior reports linking inflammatory activation and oxidative stress to repolarization abnormalities. Curcumin, despite its known antioxidant and anti-inflammatory effects, further increased QTc prolongation in combination with nilotinib. This suggests that drug–supplement interactions can modify cardiac electrophysiology. In addition, the bioavailability and complex pharmacokinetics of curcumin may have influenced the observed outcomes, indicating that exposure–effect relationships should be integrated into future experimental designs. Plasma drug level measurements and metabolite profiling will be important in clarifying this association in subsequent studies. Despite its well-established antioxidant and anti-inflammatory properties, co-administration of curcumin exacerbated nilotinib-induced QTc prolongation. This paradoxical outcome suggests a synergistic blockade of hERG channels or other repolarizing currents when combined with TKIs. Furthermore, the emergence of negative T waves and PR interval prolongation in the combination group indicates increased repolarization dispersion and atrioventricular conduction delays—both known proarrhythmic substrates (Vandenberg *et al*., 2012).

In contrast, nicorandil, a KATP channel opener with established vasodilatory and antiarrhythmic properties, demonstrated a protective effect by attenuating QTc prolongation both when administered alone and in combination with nilotinib and curcumin. The shortening of the QTc interval observed following nicorandil treatment likely reflects its ability to stabilize myocardial repolarization via KATP channel activation. The shortening of QTc and partial normalization of PR interval observed with nicorandil indicate a robust stabilization of myocardial repolarization and conduction, highlighting its potential as an effective adjunct to mitigate TKI-induced electrophysiological disturbances (Huang, 2017; Khan and Gowda, 2004). However, conflicting evidence exists regarding nicorandil's efficacy in QT shortening, with some studies reporting limited or no antiarrhythmic effects (Komori *et al*., 1985). The expected inverse relationship between heart rate and QTc duration was also observed, consistent with physiological principles whereby

bradycardia may contribute to QT prolongation (Davey and Bateman, 1999). Minor QRS prolongation was observed but lacked clinical significance; however, prolonged QRS has been associated with increased mortality in chronic cardiac pathologies (Breidthardt *et al*., 2007). The PR interval was prolonged following curcumin administration and partially normalized with nicorandil co-administration. Since PR prolongation reflects atrioventricular conduction delays, this observation may have clinical implications, particularly in patients at risk for atrial arrhythmias (De Bie *et al*., 2020). Various studies have reported conflicting effects of nilotinib on the oxidant/antioxidant system and inflammatory markers. TNF-α is a key marker of oxidative capacity and inflammation (Gupta *et al*., 2013). Importantly, no significant histopathological alterations were detected, suggesting that electrophysiological and biochemical changes may precede structural cardiac damage, indicating early-stage cardiotoxicity.

Although some studies have reported antioxidant and anti-inflammatory benefits of nilotinib at certain doses (Zhou *et al*., 2013; Ateyya *et al*., 2017), cardiotoxic effects were suggested to predominate at the administered dose, particularly under conditions of concomitant curcumin administration. However, other reports indicate that at supratherapeutic concentrations, nilotinib may increase ROS production and cell death (Doherty *et al*., 2013). It has been reported that *in-vitro* toxicity was not observed at therapeutic doses in cardiomyocytes (Wolf et al., 2010). *In vivo*, long-term administration at high doses resulted in increased heart weight, without accompanying histopathological or functional changes. It was demonstrated that even low-dose nilotinib significantly prolongs QTc in rats and increases TNF-α levels. This effect is worsened by curcumin co-treatment, likely due to shared K^+ channel inhibition. Nicorandil reversed QTc prolongation both alone and in combination, indicating cardioprotective potential. Given nilotinib's black box warning for QT prolongation and the common use of supplements like curcumin in oncology, such combinations may carry unrecognized electrophysiological risks, highlighting the importance of QTc monitoring (Moslehi, 2016). Curcumin, while cardioprotective alone, may exacerbate QTc prolongation with TKIs, requiring cautious risk-benefit assessment in clinical use.

From a pharmacovigilance perspective, potential interactions between cardiotoxic drugs and herbal supplements such as curcumin should not be overlooked. In patients receiving nilotinib–curcumin combinations, regular monitoring of QTc and, when appropriate, adjustment of ECG protocols may be warranted. In our study, even low-dose nilotinib prolonged the QTc interval and increased TNF-α levels. Co-administration of curcumin further exacerbated these effects, whereas nicorandil reversed QTc prolongation and the associated biochemical alterations. These findings suggest that nicorandil may serve as a potential cardioprotective agent against acute TKI-induced effects. Clinical caution is therefore advised when tyrosine kinase inhibitors are used concomitantly with supplements such as curcumin.

CONCLUSION

This study demonstrates that nilotinib induces significant QTc prolongation, accompanied by inflammatory and oxidative cardiac changes, likely through hERG channel inhibition. Curcumin, though typically considered cardioprotective, unexpectedly worsened QTc prolongation, suggesting a potential synergistic blockade of potassium channels. These findings raise safety concerns for cancer patients using curcumin alongside TKIs. Conversely, nicorandil effectively mitigated QTc prolongation and associated biochemical alterations, likely via activation of KATP channels, supporting its role as a cardioprotective adjunct during QT-prolonging therapies. While the acute design, male-only model, and lack of arrhythmic endpoints limit generalizability, the telemetric ECG provided robust translational data. Further studies should address chronic effects, sex differences and arrhythmia risk. Clinical trials are needed to validate nicorandil's protective role and clarify the cardiac safety of commonly used supplements such as curcumin. Overall, these results underscore the importance of integrated cardiotoxicity monitoring in oncology.

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None

Authors' contributions
NH and BS: Conceived the idea and planned the manuscript; NH, ZK and EE: Contributed to sample preparation; CCU: Carried out statistics; NH, SY and BS: Extended significant scientific support and also contributed to the interpretation of the results. All authors provided significant contributions by giving feedback and helped shape the manuscript.

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Data availability statement
The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethical approval
This study was approved by the Eskişehir Osmangazi University Local Ethics Committee for Animal Experiments (10.12.2018/681-1). This study was performed in adherence with the ARRIVE guidelines. See supplementary file for the ARRIVE checklist.

Conflict of interest
The authors declared no conflicts of interest.

Supplementary data

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