

## The effects of rutin and quercetin on ECG parameters in 5-FU-induced cardiotoxicity rat model

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### Abstract

5-fluorouracil (5-FU), a pyrimidine analogue anticarcinogenic agent, is widely used in the solid tumors treatment. Use of the 5-FU causes cardiotoxicity. Our aim in this study investigations effects of Quercetin and Rutin on ECG parameters in the 5-FU-induced cardiotoxicity in rats. In the present study used male rats. Rats were divided randomly to eight group. The control group was given intragastric corn oil for 14 days. The 5-FU group rats were given ig corn oil for 14 days and injected intraperitoneal the single dose of 5-FU(50 mg/kg) on the eleventh day. The Q50+5-FU and Q100+5-FU groups were given ig 50 mg/kg and 100 mg/kg Q for 14 days, respectively and these groups were injected single dose of 5-FU(50 mg/kg) on the 11th days of Q application. The group Q100 was Q(100 mg/kg-ig) for 14 days. The Rutin50+5-FU and Rutin100+5-FU groups were injected ig 50 mg/kg and 100 mg/kg of the Rutin for 14 days, respectively. These groups were injected single dose of 5-FU(50 mg/kg) in the 11th days of Rutin application. The Rutin 100 group was given Rutin(100 mg/kg-ig) for 14 days. In the end of experimental application recorded to ECGs of the rats. 5-FU administration rats were observed that it was caused sinus tachycardia and ST elevation. Also, in the 5-FU group QRS segment was shorter and the duration and amplitude of the P was different from other groups. In both doses of Q and Rutin were prevented these changes and our findings were seen the consistent with the literature.

**Keywords:** 5-FU; ECG; Quercetin; Rutin; Rat

### 1. Introduction

5-fluorouracil (5-FU) is an agent with fluoropyrimidine antimetabolite, which is widely used in pancreatic and skin cancer treatment (1). Gastrointestinal and hematologic toxicities are one of the most common side effects of the 5-FU (2). Cardiotoxicity, well recognized for other antineoplastic agents, is major complication of 5-FU and the cardiotoxicity resulting from use of 5-FU is characterized by angina, pulmonary edema, congestive heart failure, myocardial infarction, ventricular arrhythmias, myocardial ischemia and sudden death (3-6). The recent studies have reported that has increased cardiotoxicity cases due to 5-FU (7). The 5-FU's itself or its metabolites are toxic for myocytes (8) and Fluorouracil uptake into the myocardium has been demonstrated (9, 10). The animal studies has showed positive chronotropic and inotropic effects of 5-FU (11) and the heart rates have founded to elevate during 5-FU administration (12). It has reported that in the 5-FU treatment occurs acute global left ventricular dysfunction. In the first cycle of administration of 5-FU infusions prone to become the cardiotoxicity the patient (13) and the symptoms is initiation nearly 12 h following of the infusion (14). To prevent or treat the toxic effects of anticancer agents as 5-FU are commonly used different antioxidant compounds. Quercetin (Q) and Rutin, are natural flavonoids, have strong antioxidant effects, which available in many fruits and vegetables (15-22). The aim of the present study, investigations effects of Q and Rutin on ECG parameters in the 5-FU-induced cardiotoxicity in rats.

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## 2. Material and methods

In the study, 80 piece adult male Sprague Dawley rats was used, whose weights were 220-250 g. All the animals were housed under standard environment conditions and were allowed access to a standard diet and ad libitum drinking water. The rats were randomly divided into eight groups and there was 10 rats in each group. The control group was given only intragastric (i.g.) solvent (corn oil) for 14 days. The 5-FU group was given i.g. corn oil for 14 days and single-dose intraperitoneal (i.p.) 5-FU (50 mg/kg) was injected on the 11th day of the study. The Q50+5-FU and Q100+5-FU groups were administered i.g. the 50 and 100 mg/kg doses of Q dissolved in corn oil for 14 days and injected single dose (50 mg / kg, i.p.) of 5-FU on the 11th day. The Q100 group was given Q (100 mg/kg, i.g.) for 14 days. The Rutin50+5-FU and Rutin100+5-FU groups were given i.g. doses of 50 and 100 mg/kg of Rutin dissolved in corn oil for 14 days, respectively and single dose (50 mg / kg, i.p.) of 5-FU was administered on the 11th day. The Rutin100 group was given Rutin (100 mg/kg, i.g.) for 14 days. On the 15th day of the experiment, the ECG of the rats in all groups were recorded with cardiograf 6851 (Nihon Kohden Cardiofax C (ECG-2150), Tokyo, Japan).

### 2.1. Electrocardiographic measurements

In all derivations were used crocodile electrodes. Electrodes were placed on the elbow joints in the front skirts, just above the knee joints in the back skirts and bipolar extremity derivations (I, II and III) and increased unipolar extremity derivations (aVR, aVL and aVF) were recorded. After 72 hours from 5-FU treatment, ECG tracings (lead II) were recorded by means of an electrocardiograph connected to crocodile electrodes in rats. Nihon Kohden Cardiofax C (ECG-2150) connected to an acquisition data system was used to record and monitor ECG tracings. Analysis of ECG tracings was measured the duration of the P, P-Q, QRS, Q-T and T intervals, QRS voltage and heart rate. These ECG parameters are considered to be predictive of cardiac damages induced by 5-FU treatment. Electrocardiograms were taken with crocodile electrodes. Electrodes were placed the connecting sections to the body of the front and back legs. The areas where the electrodes were placed were thoroughly fixed with electrode gel. ECGs were taken in a quiet environment after the rats are expected to calm down. Bipolar extremity derivations were recorded six derivations as the right anterior and left anterior leg I. derivation, the right anterior and left posterior leg II. Derivation, the left anterior and left posterior leg III. Derivation and increased unipolar extremity (aVR, AVL, AVF) derivations.

### 2.2. Statistical analysis

All data were statistically evaluated by one-way ANOVA using SPSS 20.00, followed by Tukey test. The data were expressed as mean±SD.  $p < 0.05$  was considered statistically significant.

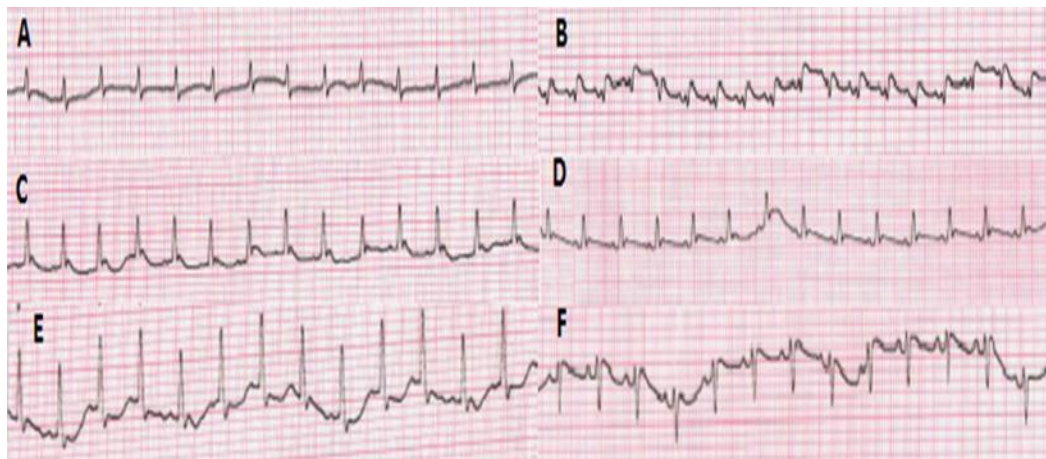
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## 3. Results

In the ECG parameters recorded from the rats in the experimental groups, the mean heart rates of the rats in the control group was determined as  $252 \pm 14$ . The number of heart beat in the 5-FU group was  $314 \pm 17$  and 5-FU caused sinus tachycardia. Also, in the 5-FU group was observed ST elevation. It was determined that both doses of Q and Rutin were prevented the sinus tachycardia caused by 5-FU ( $P < 0.05$ , Fig and Table). The heart rate numbers of rats in Q100 and Rutin100 groups did not change ( $P > 0.05$ , Fig and Tab). The duration and amplitude of the P wave in the ECG trays obtained from the groups did not different among the groups, But there was a difference in the 5-FU group ( $P < 0.05$ , Fig). The time of interval and QRS segment was shorter in the 5-FU group.

**Table 1** The effect of Q and Rutin on 5-FU-induced alterations in ECG.

Parameters	Control	5-FU	Rutin50+5-FU	Rutin100+5-FU	Q50+5-FU	Q100+5-FU	Rutin100	Q100
P (s)	0.02±0,00	0.02±0,00	0.02± 0,00	0.02± 0,00	0.02±0,00	0.02±0,00	0.02±0,00	0.02±0,00
P (mV)	0.1±0,00	0.1± 0,00	0.1± 0,00	0.1± 0,00	0.1±0,00	0.1± 0,00	0.1± 0,00	0.1± 0,00
P-Q (s)	0.04±0,00	0.03±0,00*	0.04± 0,00	0.04± 0,00	0.04±0,00	0.04±0,00	0.04±0,00	0.04±0,00
QRS (s)	0.06±0,00	0.05±0,00*	0.06± 0,00	0.06± 0,00	0.06±0,00	0.06±0,00	0.06±0,00	0.06±0,00
QRS (mV)	0.5±0,00	0.2±0,00**	0.8± 0,00**	0.7± 0,00**	0.6±0,00*	0.6±0,00*	0.8±0,00**	0.6±0,00*
Q-T (s)	0.08±0,00	0.07±0,00	0.076± 0,00	0.076± 0,00	0.08±0,00	0.08±0,00	0.08±0,00	0.077±0,00
T (s)	0.03±0,00	0.03±0,00	0.03± 0,00	0.03± 0,00	0.03±0,00	0.03±0,00	0.03±0,00	0.03±0,00
T (mV)	0.1±0,00	0.1± 0,00	0.1± 0,00	0.1± 0,00	0.1±0,00	0.1± 0,00	0.1± 0,00	0.1± 0,00
Heart rate (beats/min)	252±14	324±17**	280±15	235±23	280±15	269±16	240±17	240±18
Electrical axis (degrees)	48±10	45±9	43±7	42±5	43±8	45±10	46±8	44±9

**Figure 1** EKG traces of the Control (A), 5-FU (B), Q50+5-FU (C), Q100+5-FU (D), RUTIN50+5-FU (E), RUTIN100+5-FU (F) (n=10, p<0.05).

#### 4. Discussion

5-flourouracil (5-FU) has been commonly used as chemotherapeutic in the treatment of gastrointestinal malignancies for years. Unfortunately, as well as its beneficial antitumor effects, 5-FU also have the some toxicities which cardiotoxicity is one of these toxicities (23). The some flavonoids are widely used in researches for to prevent or treat the possible side effects of anticancer agents (24-28). The Q and Rutin compounds used for this purpose is found in the

structure of many fruits and plants (18, 19). In this study, in the 5-FU-induced cardiotoxicity model in rats was determined the possible protective effects of Q and Rutin. ECG is a frequently used parameter in the evaluation of cardiac function. One of the methods currently used for the early detection of anticancerogens-induced cardiotoxicity is ECG measurement. Cardiac side effects of 5-FU, which an anticancer agent, are rhythm abnormalities, supraventricular and ventricular dysrhythmias (29) and acute myocardial infarction was also reported in the literature (30). It has reported that in nearly 88% of patients receiving infusions of 5-FU have determined the troponin release, asymptomatic ECG changes and in approximate 68%, ST-segment deviation and QT-prolongation has observed (11, 14 ). Also, the studies has showed that the heart rates have elevated with positive chronotropic and inotropic effects of 5-FU (12).

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## 5. Conclusion

In our study, 5-FU administration rats were observed that it was caused sinus tachycardia and ST elevation. Also, in the 5-FU group QRS segment was shorter and the duration and amplitude of the P was different from other groups. 5-FU-induced ECG changes in rats were determined for the first time in our study. In both doses of Q and Rutin were prevented these changes.

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## Compliance with ethical standards

### *Acknowledgments*

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### *Disclosure of conflict of interest*

The authors declare that there are no conflicts of interest.

### *Statement of ethical approval*

Animal experiments were performed in accordance with the national guidelines for the use and care of laboratory animals and were approved by the Local Ethics Committee of Ataturk University for Animal Experiments (Protocol no: 2017/72).

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