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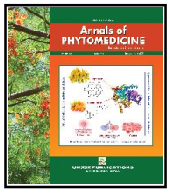

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Nanoquercetin potentially attenuates sodium fluoride induced oxidative stress mediated cardiotoxicity in rats

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Abstract

In comparison to regular quercetin, this study sought to assess the effectiveness of nano-converted quercetin in mitigating sodium fluoride-induced cardiotoxicity in a rat model. Nanoquercetin (NQC) displayed a spherical morphology, with an average particle size of 240.8 nm. In the present study, random assignment was used to divide the 24 Wistar rats into four groups of six. Exposure to sodium fluoride alone markedly raised cardiac troponin levels, serum total cholesterol, triglycerides, and lipid peroxidation, while reducing the functions of main antioxidant enzymes (superoxide dismutase, reduced glutathione, glutathione peroxidase, and catalase), along with prolonging QT and QRS intervals in the electrocardiogram. The administration of both normal quercetin and NQC significantly reduced the toxicity produced by sodium fluoride and preserved the normal histological architecture of the heart tissues. The extent of the effects suggests that NQC possesses greater therapeutic potential compared to normal quercetin, even at lower dosage levels.

1. Introduction

Fluoride is an abundant trace element found in nature and produced by both industrial and natural processes. Drinking water is one of the main sources of fluoride contamination, posing a serious public health concern in India and worldwide (Susheela and Bhatnagar, 2002). Chronic exposure to fluoride through contaminated drinking water affects teeth and bones and has detrimental effects on other vital organs, such as the heart and vascular tissues (Chattopadhyay *et al.,* 2010). Furthermore, it has been demonstrated that fluoride directly harms the cardiovascular system. Epidemiological research has linked exposure to fluoride with a higher incidence of cardiovascular complications such as arteriosclerosis, hypertension, ischemia, and cardiac failure (Amini *et al.,* 2011; Sun *et al.,* 2013). Additionally, animal studies have shown that fluorosis can lead to impaired cardiac function and pathological lesions in both myocardial and vascular tissues (Donmez and Cinar, 2003; Cicek *et al.,* 2005; Miltonprabu and Thangapandiyan, 2015). Oxidative stress is a critical factor that exacerbates organ damage caused by various environmental contaminants. The production of free radicals is widely recognized as a key mechanism associated with fluoride-mediated toxicity. Moreover, fluoride can influence the activity of various enzymes that are part of the cellular antioxidant system, including SOD, CAT, GSH, and GPx (Miltonprabu and Thangapandiyan, 2015). This interference leads to modifications in the cellular antioxidant defenses, ultimately resulting in oxidative stress.

Nowadays, natural herbal phytomolecules are used as a remedy for toxicity associated with environmental pollutants. Quercetin (QC), recognized as a polyphenolic compound, is an herbal flavonoid known for its positive impact on a wide range of cardiovascular complications (Arts and Hollman, 2005; Amsa *et al.,* 2024). Numerous studies have documented the diverse biological and pharmacological effects of QC, including its anticancer, antioxidant, antidepressant, antiviral, anti-inflammatory and analgesic properties (Nabavi *et al.,* 2012; Singh *et al.,* 2023). QC holds significant potential as an effective and safe compound with various medicinal benefits.However, there are notable drawbacks regarding its therapeutic efficacy, including limited bioavailability of QC when taken orally and rapid elimination from the body (De Boerm and Dihal, 2005).A promising approach to enhance drug delivery involves the conversion of phytomolecules into nanoparticles which exhibit enhanced pharmacological impacts on both people and animals. Thus, the study's objective is to assess how well nanoquercetin (NQC) protects Wistar rats from sodium fluoride-induced cardiotoxicity.

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2. Materials and Methods

2.1 Preparation and characterization of nanoquercetin

The preparation along with characterization of quercetin nanoparticles has been presented in our earlier report (Ayushi Chourasia *et al.,* 2024). For further characterization, we assessed the solubility of quercetin nanoparticles.

2.2 Experimental animals and design

Rats were randomly divided into four groups of six each, each weighing between 80 and 100 g. The untreated control is represented by Group I. Group 2 was subjected to daily exposure to sodium fluoride at a concentration of 100 ppm in their drinking water for 42 days. During the same 42-day period, Groups III and IV received 100 ppm of sodium fluoride in addition to oral gavages of 50 mg/kg for QC and 25 mg/kg for NQC, respectively. The Veterinary College and Research Institute in Namakkal's Institutional Animal Ethics Committee (IAEC 10/VCRI-NKL 2021) approved the study protocols.

2.3 Electrocardiographic examination

Electrocardiogram (ECG) recordings were recorded in anaesthetized rats on 42 days of treatment using a 4-lead single-channel ECG machine (CARDIART GenX1 Electrocardiograph, India). Anesthesia occurred in the rodents through administering xylazine (10 mg/kg) along with ketamine (75 mg/kg) intraperitoneally. A standard lead II ECG was recorded while the instrument was set to a paper speed of 50 mm/s (Ayushi Chourasia*et al.,* 2024).

2.4 Blood and tissue collection

On the 43rd day, using a capillary tube, various blood samples have been collected within the retro-orbital plexus to be stored in vials containing clot activator for the assessment of serum biochemical markers. Following blood collection, the rats were euthanized through cervical dislocation. The hearts were removed from each subject and weighed. Half of the excised heart tissues remained at -20 °C and were cleaned with physiological saline to quantify the levels of oxidative stress and antioxidant enzymes. Fixation was accomplished by employing a 10% neutral buffered formalin solution to determine the histological changes.

2.5 Serum biochemical markers

Collected blood in the clot activator tubes was allowed to clot for approximately 20 min, after which the serum was separated by centrifuging at 1500 revolutions per minute (RPM) for 15 minutes. The biochemical parameters, including total cholesterol, triglycerides, ALP, CK, AST, and ALT, were measured using M/s. A50 Biosystems, India.

2.6 Cardiac troponin estimation

Estimation of cardiac troponin was performed by measuring the proteins associated with troponins, which are included in the total salt-soluble proteins that are discharged during acute myocardial injury, following the method described by Bhaskar and Rao (2002). Standard procedures have been carried out to quantify the total protein content (Lowry *et al.,* 1951).

2.7 Cardiac markers of oxidative stress

Lipid peroxidation (LPO) in connection with malondialdehyde generation was evaluated using the amount of thiobarbituric acid-reactive molecules (Shafiq-Ur-Rehmn 1984). The antioxidant markers like superoxide dismutase (SOD), catalase (CAT), reduced glutathione (GSH) and glutathione peroxidase (GPx) activities were measured as per standard procedure described by Marklund (1974); Aebi (1984); Sedlak and Lindsay (1968); Paglia and Valentine (1967), respectively.

2.8 Histopathology of heart tissue

Hematoxylin and eosin were used to stain the paraffin-embedded blocks of heart tissue for histopathological examination.

2.9 Statistical analysis

The data were analyzed using ANOVA followed by Duncan's multiple range test to determine significant differences among groups. The value was given as mean ± SE. Using the following formula, the protective impact of QC and NQC was evaluated.

$$\text{Amelioration (\%)} = \frac{\text{(Pro-oxidant group – Antioxidant group)}}{\text{(Control – Pro-oxidant group)}} \times 100$$

3. Results

3.1 General observations and heart weight

There were no observable clinical signs or symptoms and mortality in all the experimental rats throughout the study. There were no macroscopical changes in the heart. Additionally, there was no significant alteration in the absolute as well as relative weight of the heartin various treatments (data not shown).

3.2 Effect on electrocardiography (ECG)

Rats subjected to different ECG parameters and the impact of QC and NQC fluoride are detailed in Table 1.In comparison to the control, the amplitude of the P wave, mean duration (s) of the heart rate, P wave, QRS complex, P-R interval, and Q-T interval all markedly increased in rodents that were exposed to fluoride. NQC significantly restored the mean duration (s) of heart rate, Q-T interval, and P-R interval, while QC did not substantially modify the fluoride-induced alterations in the ECG in comparison to the fluorideonly treated group.

3.3 Serum cardiac enzymes

ALT, AST, ALP, CK and cardiac troponin levels had markedly risenin rats exposed to fluoride (Table 2). QC and NQC treatment significantly reduced the fluoride-induced cardiac marker levels in rats. Nevertheless, no significant difference was observed between QC and NQC treatment, but the amelioration percentage was high in NQC treatment.

3.4 Effects on serum lipid profile

Table 3 illustrates the variations in blood lipid levels observed in both control and treatment groups. Blood triglyceride and cholesterol levels significantly increased in rats that were exposed to fluoride (Table 3). NQC treatment resulted in decreased serum cholesterol and triglyceride levels. Although, NQC treatment was not statistically significant from QC treatment, but amelioration percentage was high in the NQC treatment.

Table 1: Effect of quercetin and nanoquercetin on electrocardiogram parameters of rats given continuous exposure to sodium fluoride

Group	Treatment	Dose/ Concentration	P wave amplitude (mv)	QRS complex duration (s)	P-R interval duration (s)	Q-T interval duration (s)	S-T interval duration (s)	Duration (s)	Heart rate (beats/min)
I	Control	Water	0.05 ± 0.02^{c}	0.010 ± 0.02^{b}	0.010 ± 0.01^{b}	0.05 ± 0.002^{b}	0.04 ± 0.00^{c}	0.02 ± 0.006	330.00 ± 3.65^{bc}
II	Fluoride	100 ppm + MC	0.10 ± 0.01^{b}	0.020 ± 0.04^{a}	0.020 ± 0.01^{a}	0.06 ± 0.002^{a}	0.05 ±0.00^{b}	0.02 ± 0.005	393.33 ± 19.09^{a}
III	Fluoride + QC	100 ppm + 50 mg/kg	0.10 ± 0.02^{b}	0.020 ± 0.03^{a}	0.020 ± 0.01^{a}	0.06 ± 0.001^{b}	0.06 ± 0.00^{a}	0.02± 0.002	340.00 ± 2.58^{c}
IV	Fluoride + NQC	100 ppm + 25 mg/kg	0.15 ± 0.01^{a}	0.020 ± 0.02^{a}	0.020 ± 0.01^{a}	0.05 ± 0.002^{b}	0.04 ± 0.00^{c}	0.02 ± 0.006	330.00 ± 2.58^{b}

Values are expressed as mean ± SE (n=6). Values in the same column bearing common superscript did not vary significantly (p<0.05) in Duncan's multiple comparison test.

Table 2: Effect of quercetin and nanoquercetin on serum cardiotoxic markers of rats given continuous exposure to sodium fluoride

Treatment	Dose/ Concentration	ALT (IU/L)	AST (IU/L)	ALP (IU/L)	CK (IU/L)	Troponin level (ng/ml)
Control	Water	54.17 ± 3.21^{d}	106.17 ± 6.63^{c}	198.33 ± 24.87^{b}	1098.67 ± 51.00^{c}	25.80 ± 2.14^{d}
Fluoride	100 ppm + MC	206.83 ± 4.33^{a}	283.33 ± 18.34^{a}	387.17 ± 21.48^{a}	2596.67 ± 133.19^{a}	48.39 ± 2.08^{a}
Fluoride + QC	100 ppm + 50 mg/kg	106.33 ± 16.24^{c}	177.33 ± 11.35^{b}	238.83 ± 25.60^{b}	1040.83 ± 81.63^{c}	35.73 ± 4.23^{b}
Fluoride + NQC	100 ppm + 25 mg/kg	112.67 ± 16.13^{bc}	121.67 ± 5.82^{c}	217.67 ± 26.94^{b}	1138.83 ± 169.75^{c}	29.39 ±4.18^{bc}

Values are expressed as mean ± SE (n=6). Values in the same column bearing common superscript did not vary significantly (p<0.05) in Duncan's multiple comparison test.

Table 3: Effect of quercetin and nanoquercetin on the level of serum total cholesterol and total triglyceride of rats given continuous exposure to sodium fluoride

Treatment	Dose/Concentration	Total cholesterol (mg/dl)	Total triglyceride (mg/dl)
Control	Water	169.17 ± 15.62^{b}	94.67 ± 7.23^{b}
Fluoride	100 ppm + MC	315.67 ± 6.75^{a}	174.00 ± 13.18^{a}
Fluoride + QC	100 ppm + 50 mg/kg	206.83 ± 22.23^{b}	102.50 ± 14.04^{b}
Fluoride + NQC	100 ppm + 25 mg/kg	203.83 ± 20.88^{b}	97.83 ± 5.25^{b}

Values are expressed as mean ± SE (n=6). Values in the same column bearing common superscript did not vary significantly (p<0.05) in Duncan's multiple comparison test.

3.5 Effects on lipid peroxidation

Rats exposed to fluoride had significantly higher cardiac LPO levels than the control group (Table 4). The LPO level in cardiac tissue significantly decreased after QC and NQC were administered, with drops of 66 and 90%, respectively. Although, the difference between NQC and QC treatments were not statistically significant, but amelioration percentage was high in the NQC treatment.

3.6 Effects on the antioxidantenzymes

Table 5 shows that sodium fluoride exposure caused a notable decrease in the heart tissue's GSH and GPx activity. QC treatment significantly increased GSH and GPxactivities by 53% and 44%, respectively, whereas NQC treatment also increased the GSH and GPxactivities in cardiac tissue by 74% and 58%. However, the percent amelioration was high in NQC treatment in fluoride exposed rats.

Table 4: Effect of quercetin and nanoquercetin on lipid peroxidation (nmole MDA formed/g tissue) in heart tissue of rats given repeated exposure to sodium fluoride

Treatment	Dose/Concentration	LPO	Amelioration (%)
Control	Water	0.80 ± 0.38 ^{b}	
Fluoride	100 ppm + MC	2.97 ± 0.20 ^{a}	
Fluoride + QC	100 ppm + 50 mg/kg	1.50 ± 0.22 ^{b}	66
Fluoride+ NQC	100 ppm + 25 mg/kg	1.08 ± 0.22 ^{b}	90

Values are expressed as mean ± SE (n=6). Values in the same column bearing common superscript did not vary significantly (p<0.05) in Duncan's multiple comparison test.

Table 5: Effect of quercetin and nanoquercetin on the activity of glutathione peroxidase (µmole of NADPH oxidized to NADP/mg of protein/min) and reduced glutathione (mM of GSH per g of wet tissue) in the heart tissue of rats given continuous exposure to sodium fluoride

Treatment	Dose/ Concentration	Glutathione peroxidase	Amelioration (%)	Reduced glutathione	Amelioration (%)
Control	Water	33.98 ± 5.17[a]	-	57.98 ± 3.03[a]	-
Fluoride	100 ppm + MC	12.98 ± 0.71[b]	-	24.82 ± 2.58[b]	-
Fluoride + QC	100 ppm + 50 mg/kg	22.26 ± 2.68[bc]	44	42.61 ± 3.50[c]	53
Fluoride + NQC	100 ppm + 25 mg/kg	25.22 ± 4.65[ac]	58	49.45 ± 3.73[ca]	74

Values are expressed as mean ± SE (n=6). Values in the same column bearing common superscript did not vary significantly ($p<0.05$) in Duncan's multiple comparison test.

3.7 Effects on SOD and CAT

Table 6 demonstrates the cardiac SOD and CAT activities of experimental and control rats. SOD and CAT activities in cardiac tissue were significantly reduced in rats exposed to fluoride. Treatment with QC resulted in a significant enhancement of SOD activity by 36% and CAT activity by 52%. In contrast, NQC treatment produced a substantial increase in SOD activity by 86% along with CAT activity by 70% in the cardiac tissue. However, the effect of NQC treatment did not differ significantly from QC treatment, but the amelioration percentage was higher in NQC treatment.

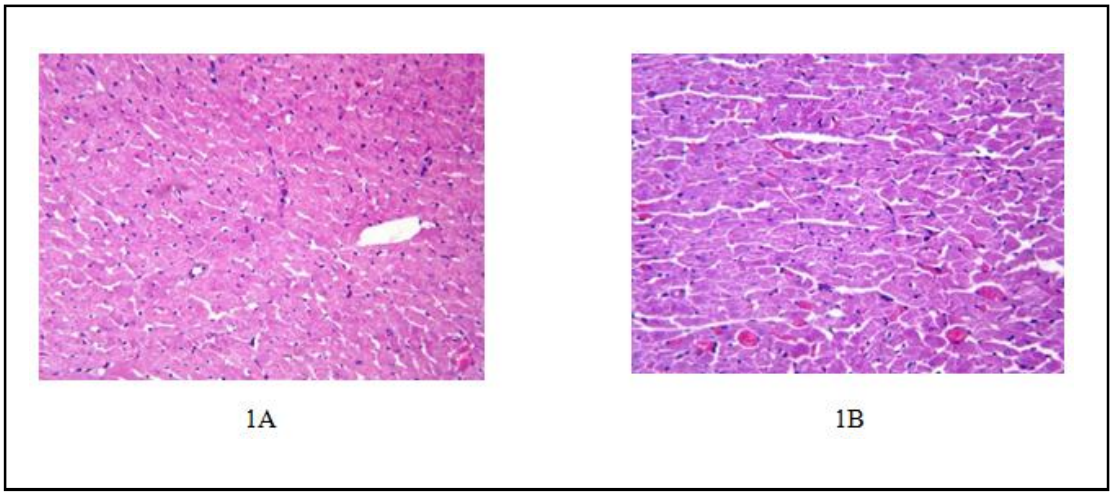
Table 6: Effect of quercetin and nanoquercetin on the activity of superoxide dismutase (Units/mg protein) and catalase (mmole H_2O_2 utilized/min/mg protein) in the heart tissue of rats given continuous exposure to sodium fluoride

Treatment	Dose/ Concentration	Glutathione peroxidase	Amelioration (%)	Reduced glutathione	Amelioration (%)
Control	Water	26.22 ± 1.87[a]	-	1.61 ± 0.13[a]	-
Fluoride	100 ppm + MC	10.68 ± 0.79[b]	-	0.50 ± 0.08[b]	-
Fluoride + QC	100 ppm + 50 mg/kg	17.75 ± 3.08[c]	36	1.12 ± 0.16[ac]	52
Fluoride + NQC	100 ppm + 25 mg/kg	24.08 ± 2.98[c]	86	1.30 ± 0.30[ac]	70

Values are expressed as mean ± SE (n=6). Values in the same column bearing common superscript did not vary significantly ($p<0.05$) in Duncan's multiple comparison test.

3.8 Histopathology of the heart

The heart tissue in the control group lacked any significant microscopic alterations and revealed normal histologic details (Figure 1 A and B). Heart tissue of the fluoride exposed group showed mononuclear cell infiltration at the epicardium of the left atrium (Figure 1C) and also revealed swollen myocardial fibers with degeneration and mononuclear cell infiltration at the epicardium of the left ventricle (Figure 1D). Treatment with QC in fluoride exposed rats of heart tissue revealed moderate degeneration and necrosis with mononuclear cell infiltration at the left ventricle epicardium (Figure 1E) and the blood vessels (Figure 1F). However, treatment with NQC in fluoride exposed rats of heart tissue showed mild degeneration and congestion of blood vessels in the myocardium (Figure 1G and H).



1A 1B

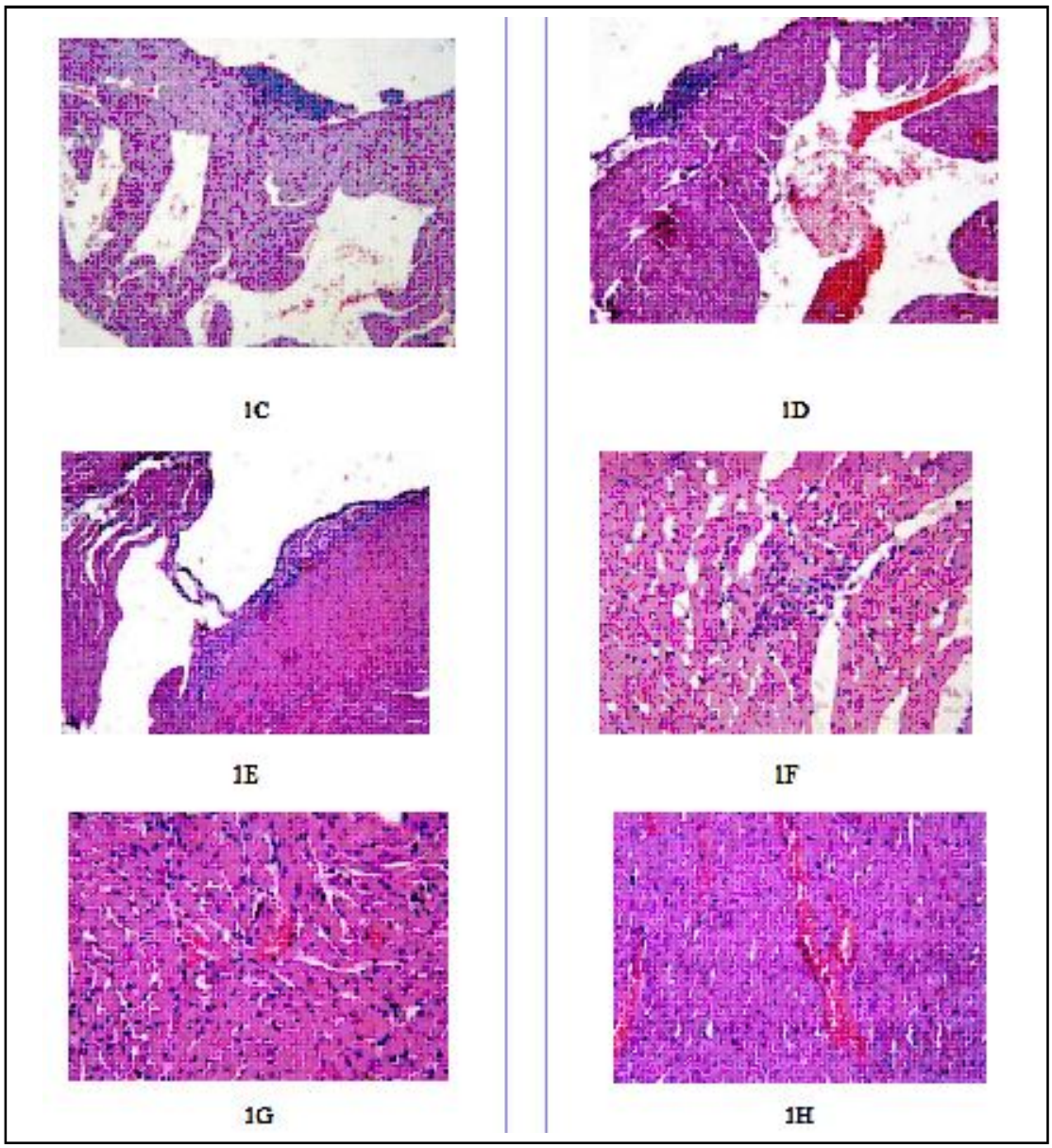


Figure 1: Effect of QC and NQC on histopathological changes in heart tissue of rats given repeated exposure to fluoride.

4. Discussion

NQC was prepared by using the nanoprecipitation technique, yielding particles with an average size of 220 ± 20 nm, therebyconfirming the successful conversion of the prepared QC into its nanoform. In the present study, the lyophilized nanoquercetin powder was resuspended in water, formed a very fine dispersion and appeared to be soluble. However, the original QC is completely insoluble in water. The reduction of phytomolecule particle size increases the surface area which leads to better dissolution in water and thereby more bioavailability. Accordingly, NQC produced through the nanoprecipitation method, exhibiting an improved dissolution rate, may lead to greater oral bioavailability (El-Rahman and Al-Jameel, 2014).

Fluoride toxicity significantly affects the cardiovascular system (Panneerselvam *et al.,* 2015). Fluoride mediated increase in serum ALT, AST, ALP and CK activities suggests cardiotoxic alterations associated with heightened fluoride levels in the myocardium. This accumulation can lead to loss of membrane integrity in cardiomyocytes (Panneerselvam *et al.,* 2015; Emejula *et al.,* 2016). Cardiac troponin is its myocardial tissue specific proteinthat is a highly sensitive and specific marker of myocardial damage. Moreover, it demonstrates greater efficacy compared to previous markers, as they contribute not only to diagnostic processes but also to risk evaluation and therapeutic decision-making (Peela *et al.,* 2010). Our findings indicated that elevated levels of troponin suggest the severity of fluoride induced pathological alterations in the myocardium (Abdel-Baky and Abdel-Rahman, 2020). The enzymatic modifications may be associated with the histological changes noted in the cardiac tissues.

Both QC and NQC showed improvements in the fluoride-induced alterations of these marker enzymes and histological structures. All of these discoveries are corroborated by Ismail *et al.* (2014), who documented QC's protective effects on cardiac tissues' enzymatic and histological alterations.

Lipids are significant contributors to the progression of atherosclerosis and cardiovascular diseases. Additionally, fluoride mediated cardiotoxicity is linked to elevated levels of both circulatory and cardiac lipids (Hassarajani *et al*., 2007). A prominent increase in serum total cholesterol and triglycerides observed in this study constitutes a primary risk factor for the onset of myocardial dysfunction (Miltonprabu and Thangapandiyan, 2015; Abdel-Baky and Abdel-Rahman, 2020; Abdel-Wahab, 2013). The present study suggests that both QC and NQC have a hypolipidemic impact along with defense against cardiovascular damage brought on by fluoride by stabilizing aneffect on myocardial phospholipids. However, the treatment with NQC hada more potent effect on lipid profile parameters than QC. The observed effect can be attributed to NQC hasa greater capacity to inhibit the peroxidation of membrane phospholipids. In addition, NQC could restore the alterationin lipid profiles of fluoride treatment in rodents may be associated with its antioxidant and antilipoperoxidative characteristics (Nijveldt *et al.,* 2001).

An ECG is a diagnostic procedure and a frequently used parameter in the evaluation of cardiac function. The P wave duration and amplitude are markedly elevated in rats given fluoride. Additionally, the P-R interval was significantly prolonged in fluoride exposed rats. This marked extension of the P-R interval can be attributed to a delay in impulse conduction from the sinoatrial node to the atrioventricular node. This may be linked to a substantial reduction in sodium ion concentration (Oyagbemi *et al.,* 2018). The ECG analysis showed increased QRS and Q-T intervals as well as increased heart rate in fluoride exposed rats. The variations in the QRS and Q-T intervals may be linked to hypocalcemia, which induces delayed repolarization and subsequently leads to dysrhythmias characterized by ventricular fibrillation (Oyagbemi *et al.,* 2018). Further, the prolonged durations of various waves contribute to a marked reduction in cardiac cell activity, resulting in sinus bradycardia (Kant *et al*., 2009). The current investigation indicates that NQC treatment yields positive effects on the alterations in ECG parameters and the increased heart rate associated with fluoride toxicity in rats. The antioxidant, membrane stabilizing property and restoration of serum electrolyte levels of QC makes them to restore the ECG parameters. However, the precise mechanisms through which these antioxidants alleviate ECG changes remain unclear and need further investigation.

Oxidative stress is considered one of the main mechanisms by which fluoride exposure may contribute to cardiovascular damage (Geng *et al.,* 2014). A higher LPO level suggests more reactive oxygen species are being produced, which may ultimately result in impairment of myocardial function (Thangapandiyan and Miltonprabu, 2013; Ameeramja *et al*., 2015). Both QC and NQC decreased the fluoride mediated increase in cardiac LPO. The administration of QC diminished oxidative damage, likely serving as a highly effective scavenger of reactive oxygen species since it has two antioxidant pharmacophores that help scavenge free radicals (Salehi *et al.,* 2020). More interestingly, it is evident from the result that treatment with NQC caused a better reduction of LPO levels in heart tissue. This effect suggests that nano conversion of QC may increase aqueous solubility and enhance bioavailability and bioactivity.

Maintaining a balance between antioxidants and prooxidants is essential for the normal functioning of cells (Nordberg *et al*., 2001). Studies indicate that fluoride exposure leads to a marked reduction GSH levels and a decrease in SOD, CAT, or GPx activity within its cardiac tissue (Basha and Sujitha, 2011; Miltonprabu and Thangapandiyan, 2015; Oyagbemi *et al*., 2018). The results of this investigation showed a noteworthy reduction of antioxidants along side an increase in LPO, which may be harmful to cardiac tissues (Barbier *et al.,* 2010). It was observed that QC and NQC treatment increased GSH, GPx, SOD, or CAT activity in heart tissue but the amelioration percentage was very high in treatment with NQC as compared to QC. Oyagbemi *et al*. (2018) also demonstrated that QC enhanced cardiac GSH, GPx, SOD and CAT activity in rats exposed to fluoride.

5. Conclusion

A comparison of the ameliorative effects of QC and NQC revealed that both produced statistically similar outcomes. Nevertheless, the percentage of amelioration indicated that NQC had a more significant impact than normal QC. In conclusion, this study demonstrates that NQC is more effective than normal quercetin in mitigating fluoride mediated cardiotoxicity.

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Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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