

Quercetin may repair the impaired oxidant-antioxidant balance in 1, 2, 3, 4-tetrachlorodibenzo-*p*-dioxin induced cardiac injury in male rats

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Abstract: The purpose of this study was to evaluate the prophylactic effects of quercetin (QUE) against oxidative damages and histological changes induced by 1, 2, 3, 4-tetrachlorodibenzo-*p*-dioxin (TCDD) in rat heart. For this purpose, 20 adult male Wistar rats were divided into four groups as fellow control group, TCDD group (10µg/kg BW/day by gavage daily for 60 consecutive days), QUE group (30 mg/kg BW/day) and TCDD + QUEgroup. The oxidative biomarkers of heart tissue and the levels of cTnI and lipid profile in serum were measured. Our results showed that the cTnI serum level and the heart lipid peroxidation significantly increased and the heart level of antioxidant profile significantly decreased in the TCDD group compared to control and QUEgroups. While pretreatment with QUEcould significantly improved these factors in serum and heart tissue in animals that consumed TCDD. It can be concluded that QUEat doses of 30 mg/kg/day could alleviate heart oxidative damage and histological changes induced by TCDD.

Key words: Quercetin; 1, 2, 3, 4-Tetrachlorodibenzo-*P*-Dioxin (TCDD); Oxidative stress; Heart.

Introduction

1,2,3,4-Tetrachlorodibenzo-*P*-Dioxin (TCDD) with the chemical formula $C_{12}H_4Cl_4O_2$ is the most potent polychlorinated dibenzodioxins and is a persistent organic pollutant. TCDD is a class of extremely hazardous molecules that might pose a threat to humans (1). TCDD has high lipophilicity and the little or no metabolism in human beings hence its half-life is long and 5-10 years. TCDD is a ubiquitous environmental pollutant that can adversely and biochemically affect animals and humans. Evidence from *in vivo* studies showed that acute and chronic exposure to TCDD causes hepatotoxicity, immunotoxicity, reproductive dysfunction, carcinogenesis and cardiotoxicity (2-8). Ciftci et al., (2013a) showed that TCDD (2 µg/kg) causes oxidative damage and histological changes in heart of rat (9). In addition, long-term exposure to TCDD has toxic effects on the growth and function of the cardiovascular system (10). Some of them believe that blood vessels are the main target of TCDD during the formation of larval zebrafish edema. Dose-dependent exposure to TCDD can cause cardiomyopathy and chronic active arteritis (10, 11).

The heart is a highly active organ that is constantly exposed to dissolved chemicals in the bloodstream. Most myocardial cells in this muscle tissue are occupied by mitochondria. Moreover, the energy required for the activity of this organ is produced from the oxidation of fatty acids. For these reasons, the heart is an organ prone to oxidative damage. Changes in the redox state of cells and interaction with aryl hydrocarbon (Ahr) receptor as an agonist in cytoplasm cells are the most important of basic mechanisms for toxicity induced by TCDD (12).

Ahr as a transcription factor plays a critical role in regulating the expression of many genes such as Hsp90 and cytochrome P450 (CYP1A1). Increased expression of CYP1A and CYP1B genes by Interaction of TCDD with Ahr causes the production of reactive oxygen/nitrogen species (13). Increasing the production of oxidants, especially reactive oxygen/nitrogen species, and reducing the antioxidants content, known as oxidative stress, have recently attracted a great deal of attention (12) and it is known as one of the basic mechanisms of toxicity induced by TCDD in many tissues such as liver and testis (2, 3). It has been shown that TCDD induces oxidative stress by enhancing lipid peroxidation, decreasing glutathione (GSH) content and misbalancing antioxidant enzymes in the liver and heart. Increasing the production of ROS in the cardiovascular system can be due to impaired mitochondrial function, endothelial dysfunction and auto-oxidation of catecholamines (14). Therefore, the use of herbal supplements or their products to inhibit the production of free radicals is an excellent strategy to prevent and to treat oxidative damage induced by chemicals such as TCDD (15-17).

Quercetin (3,5,7,3',4'-pentahydroxyflavone, QUE) is a plant-derived compound such as onion, grape, nuts, tea, berries, cabbage, and cauliflower that has many medicinal properties. QUEacts an antagonist for Ahr activated by TCDD (2, 3). It shows a variety of biological effects, including antioxidants, lowering blood pressure (BP) and alleviating diseases associated with hyperglycemia, as shown in animal models and to some extent in humans.

Besides, it has stimulating effects on sperm quality and reproductive organs in adult male rats. The antioxi-

dant capacity of this molecule comes from the catechol group in the B-ring and the OH group in situation 3 and is responsible for many of its beneficial effects (18). Recent studies indicated that QUE had a potent protective effect on the liver against oxidative stress in rats (19). Evidence from recent studies showed that QUE exerts the anti-ischemic and anti-inflammatory activity against cardiovascular disorders (20). Therefore, the main objective of this study was to evaluate the prophylactic effects of QUE against oxidative stress and histological damage induced by TCDD in rat heart.

Materials and Methods

Chemicals

TCDD (purity>99%) and QUE (purity>99%) were purchased from Beijing Solarbio Science & Technology Co., Ltd. (Beijing, China). All other chemicals used were obtained from the local suppliers.

Experimental animals

20 healthy adult male Wistar rats (200±15gr) were purchased from the Department of Biology, College of Education, Salahaddin University-Erbil. Animals were kept in Plexiglass cages in an animal room under controlled condition (12-h light/dark cycle and 22±2°C) and had access to pelleted food and tap water *ad libitum*. All investigations were conducted in accordance with the "Guiding Principles for the Care and Use of Research Animals" approved by Salahaddin University-Erbil with reference number: 918-761-0484.

Experimental design

Rats divided randomly into four equal groups, and treatment with QUE was given by gavage daily for 60 consecutive days: Normal control group where rats received the vehicle, i.e., 1 ml/day of corn oil. TCDD group where animals were orally administered TCDD (20µg/kg BW/day) for 60 consecutive days. QUE group, rats were treated with QUE (30mg/kg BW/day by gavage) for the same time. TCDD- QUE group where rats were treated with TCDD (20µg/kg BW/day) and QUE (30mg/kg BW/day). Body weight was measured once a week. The weight of the heart was measured after dissection and relative organ weight was calculated by the following equation: heart weight (g) × 100/body weight (g).

Sampling and tissue preparation for biochemical analysis

At the end of the study, animals were sacrificed with deep anesthesia by ether. Blood samples were collected by heart puncture and were drawn into the blood-collec-

ting tube. Sera were then collected and stored at -20°C for the assessment of biochemical factors. After sampling blood, the heart was quickly removed and washed in ice saline. It then was homogenated by a homogenizer. The homogenated tissue was missed with phosphate buffer (pH 7.4, 0.1 M) and then was centrifuged at 15000g for 10min. The upper supernatants were used for the assessment of biochemical factors.

Biochemical assessments

Evaluation of serum cardiac troponin I (cTnI)

Serum cTnI levels were measured using a Cobas-e411 analyzer (Roche Diagnostics, Mannheim, Germany).

Evaluation of serum lipid profile

The kit was provided by Pars Azmun to evaluate the serum lipid profile according to the manufacturer's instructions, including total cholesterol (TC) and total triglycerides (TG), low density lipoprotein (LDL-c) and high density lipoprotein (HDL-c) Calculate the plasma atheroma index (AIP) based on the following formula.

Evaluation of heart oxidative biomarkers

The level of Malondialdehyde (MDA) in the heart as a byproduct of lipid peroxidation was measured by a modified spectrophotometric method. The activity of antioxidant profiles such as superoxide dismutase (SOD) and catalase (CAT) along with the level of glutathione (GSH) was measured according to the manufacturer's instructions using the kit supplied by Beijing Solarbio Science & Technology Co., Ltd, Beijing, China.

Statistical Analysis

The Graph Pad Prism 6 version 6.01 for Windows (Graph Pad Software 2012) was used to analyze the results. Analyzing of results was done by one-way analysis of variance (ANOVA) followed by Tukey's multiple comparisons test. Data for this experiment were expressed as the mean ± standard deviation (SD). p≤0.05 was set as a significant difference.

Results

Body weight and cardiosomatic index (CSI)

The results showed that final body weight significantly decreased in the TCDD group compared to control (p<0.05, Table 1). The results also showed that treatment with QUE significantly increased the final weight gain in TCDD- QUEgroup compared to TCDD group (p<0.05, Table 1). The results also showed that although the level of CSI higher in the TCDD group

Table 1. The mean ± SD of BW and CSI in different groups.

Groups	Control	TCDD	QCT	TCDD- QCT
Initial Body Weight (gm)	208.56±9.80	212.28±9.78	210.96±7.84	208.64±8.81
Final Body Weight (gm)	301.42±13.83	264.44±8.26***	302.66±10.77###	292.26±10.05†††
Weight gain (gm)	92.86±8.94	52.16±9.35***	91.70±12.75###	83.62±15.41††
Weight gain (%)	44.77±6.66	24.72±5.25**	43.69±7.84##	40.33±8.91†
CSI (%)	0.338±0.09	0.412±0.04	0.323±0.04	0.349±0.04

Results indicates as mean ±SD. *, **, *** for p<0.05, p<0.01, p<0.001 (vs. control group); #, ##, ### for p<0.05, p<0.01, p<0.001, respectively (vs. TCDD group); while †, ††, ††† for p<0.05, p<0.01, p<0.001, respectively (vs. QUEgroup).

than in other groups, there is no significant difference among all groups about CSI ($p>0.05$, Table 1).

Serum cardiac troponin I (cTnI)

The evaluation of serum cardiac troponin I (cTnI) was done to represent myocardial damage. Our results showed that the serum level of cTnI significantly increased in animals where received TCDD compared to the control group ($p<0.05$, Table 2). The level of this factor significantly decreased by QUE in healthy animals compared to control. The results also showed that treatment with QUE significantly decreased the serum level of cTnI in the TCDD group compared to the TCDD group ($p<0.05$, Table 2).

Heart oxidative biomarkers

The mean \pm SD of SOD, CAT, GSH and MDA levels is present in Table 3. The activity of SOD, GSH and CAT in heart tissue significantly decreased and the heart level of MDA significantly increased in rats treated with TCDD compared to other groups ($p<0.05$, Table 3). While treatment with QUE improved the level of these oxidative biomarkers in rats with TCDD. Our results also showed that the administration of QUE cause improved the activity of SOD, CAT, GSH and MDA level in healthy animals ($p<0.05$, Table 3).

Lipid profile

Mean \pm SD for lipid profile including TG, TC, LDL, VLDL and HDL are presented in Table 4. The level of TG, TC, LDL and VLDL in serum significantly increased, and the serum HDL as the good cholesterol significantly decreased in the TCDD group compared to other groups ($p<0.05$, Table 4). Treatment with QUE

significantly increased the HDL level and decreased the level of TG, TC, LDL and VLDL in animals that consumed TCDD compared to TCDD group without any treatment ($p<0.05$, Table 4).

Histopathological results

The histopathological findings of the heart tissue in healthy and TCDD-treated rats are presented in Figure 1. No significant histological changes were observed in control and QUE groups (Figure 1 a and b). However, the administration of TCDD could change the heart tissue. Some histopathological changes were observed in the interventricular septum and the left ventricle. The

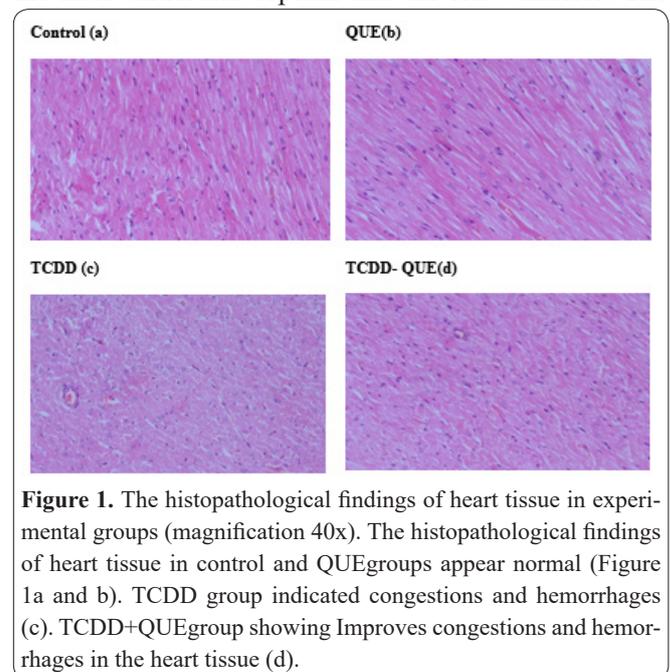


Figure 1. The histopathological findings of heart tissue in experimental groups (magnification 40x). The histopathological findings of heart tissue in control and QUE groups appear normal (Figure 1a and b). TCDD group indicated congestions and hemorrhages (c). TCDD+QUE group showing Improves congestions and hemorrhages in the heart tissue (d).

Table 2. Serum cTnI of experimental groups as compared to the control group.

Groups	Control	TCDD	QCT	TCDD- QCT
cTnI (ng/ml)	0.391 \pm 0.17	0.980 \pm 0.13***	0.234 \pm 0.09###	0.672 \pm 0.06****#††

Results indicates as mean \pm SD. *, **, *** for $p<0.05$, $p<0.01$, $p<0.001$ (vs. control group); #, ##, ### for $p<0.05$, $p<0.01$, $p<0.001$, respectively (vs. TCDD group); while \$, \$\$, \$\$\$ for $p<0.05$, $p<0.01$, $p<0.001$, respectively (vs. QUE group).

Table 3. The mean \pm SD of heart oxidative biomarkers in studied groups.

Groups	Control	TCDD	QUE	TCDD- QUE
MDA (nmol/g)	11.73 \pm 3.07	24.39 \pm 4.66***	9.49 \pm 3.82###	18.77 \pm 3.89††
GSH (μ g/g)	60.21 \pm 5.25	46.22 \pm 8.37*	69.27 \pm 7.27###	58.58 \pm 7.65
SOD (U/g)	63.12 \pm 4.72	43.18 \pm 7.47**	72.79 \pm 10.31###	57.06 \pm 6.46#†
CAT (U/g)	67.17 \pm 5.12	45.02 \pm 6.41***	74.87 \pm 5.36###	57.83 \pm 6.15#††

Results indicates as mean \pm SD. *, **, *** for $p<0.05$, $p<0.01$, $p<0.001$ (vs. control group); #, ##, ### for $p<0.05$, $p<0.01$, $p<0.001$, respectively (vs. TCDD group); while †, ††, ††† for $p<0.05$, $p<0.01$, $p<0.001$, respectively (vs. QUE group).

Table 4. Lipid profile of experimental groups as compared to the control group.

Groups	Control	TCDD	QCT	TCDD- QCT
Total cholesterol (mg/dl)	72.06 \pm 4.72	86.48 \pm 2.87***	66.58 \pm 4.84###	80.26 \pm 3.86*†††
Triglyceride (mg/dl)	65.14 \pm 5.72	76.42 \pm 4.06*	60.94 \pm 6.23###	69.46 \pm 4.24
LDL-C (mg/dl)	19.46 \pm 2.55	43.56 \pm 3.65***	14.24 \pm 1.43###	27.80 \pm 5.47*###†††
HDL-C (mg/dl)	39.08 \pm 3.76	32.62 \pm 3.34*	43.06 \pm 3.22###	37.02 \pm 1.87†
VLDL-C (mg/dl)	13.02 \pm 1.14	15.28 \pm 0.81*	12.18 \pm 1.24###	13.89 \pm 0.84
AIP	0.67 \pm 0.52	1.34 \pm 0.21	0.41 \pm 0.09	0.88 \pm 0.15

Results indicates as mean \pm SD. *, **, *** for $p<0.05$, $p<0.01$, $p<0.001$ (vs. control group); #, ##, ### for $p<0.05$, $p<0.01$, $p<0.001$, respectively (vs. TCDD group); while †, ††, ††† for $p<0.05$, $p<0.01$, $p<0.001$, respectively (vs. QUE group). The Atherogenic Index of Plasma (AIP) = (Triglycerides (mg/dl)-HDL-c (mg/dl))/HDL-c(mg/dl).

main changes included myocardial congestion, hemorrhage and edema (Figure 1c). In the TCDD+QUE group, the severity of heart histopathological changes observed was significantly improved compared to those in the TCDD group (Figure 1 d).

Discussion

The most important finding of this study is that TCDD induces cardiotoxicity by inducing oxidative damage and histological changes, and treatment with QUE can improve these harmful effects, which is consistent with previous reports (2, 9, 21). Our results indicated that the weight of the body and heart in the TCDD group changed which is in agreement with previous studies (2, 22). These studies showed that TCDD decreased the weight of the body, testicular and liver. These effects may be due to the dysfunction of hormones that regulate body weight and factors such as inflammation-induced by TCDD (23). Treatment with QUE could improve the body and heart weight in the rats treated with TCDD. Moreover, chronic and acute exposure to TCDD increased the blood pressure and the levels of serum TG and heart weight, as well as induced oxidative stress in animals (8, 24). It is possible that the improvement in body weight and heart weight after consuming QUE can be due to improve the liver damage from TCDD (21). Our results also showed that TCDD induced oxidative stress and histological changes in heart which is in agreement with previous studies (2, 5, 7, 9, 21, 22). The TCDD induces oxidative stress and histological changes in heart and liver tissues. They also showed that chrysin and quercetin could reduce the harmful effects of TCDD-induced in liver tissue (9). These authors also showed that chrysin and QUE had better effects than chrysin or quercetin alone. They also showed that protocatechuic acid could improve oxidative stress and histological changes from TCDD in the heart (9). Other studies also reported that MDA and other oxidative biomarkers increase in some organs such as kidney, thymus, testis and brain from TCDD (2, 4). Enzymatic antioxidants such as SOD, CAT, GPx and GR, along with non-enzymatic antioxidants including vitamins (A, C and E) and GSH scavenger ROS overproduction and inhibit lipid peroxidation in the biological system. In our study, results showed that TCDD induced heart oxidative damage and histological changes by decreasing the activity of SOD, CAT and GSH and increasing the MDA level. The source of oxidative damage can be dysfunction and mitochondrial structure in heart cells after exposure to TCDD (6). Moreover, our results showed that TCDD caused severe histological damages such as numerous apoptotic cells in the heart tissue which are in agreement with previous studies (5, 7, 9). The results also showed an increase in serum concentrations of cardiac troponin (cTnI) as a biomarker for myocardial damage from TCDD. Cardiac troponin T (cTnT) and cTnI are cardiac regulatory proteins that control the calcium-mediated interaction between actin and myosin. An increase in these factors indicated oxidative damage to the heart and could change the function of this organ. Some changes induced by TCDD in the function and structure of this organ can be due to change in the expression of some genes, inflammation (25), and direct effects on

calcium signaling pathways in cardiomyocytes (11). Abdulkareem and Nanakali (2020) showed that TCDD induced liver damage by changing the hepatic expression of the *CYP1A1* gene and oxidative damage (2). The *CYP1A1* gene plays an important role in the redox state of cells and the metabolism of xenobiotic compounds (26, 27). Such molecular, physiological, and morphological effects in rodent models, all cautiously, indicate a link between exposure to dioxins and mortality from cardiovascular disease.

The results also showed that TCDD could induce dyslipidemia i.e., increasing the serum levels of TG, TC, LDL and VLDL and decreasing in the serum level of HDL. The results of this study showed that TCDD increased the Atherogenic Index of Plasma (AIP) which is a predictive indicator for monitoring coronary artery disease (28), while QUE decreased it compared to other groups. As mentioned earlier TCDD increased the level of cTnI in serum. An increase in these factors indicates structural and functional damage to the heart tissue that can be due to oxidative damage.

The results of this study showed that QUE (30 mg/kg/day) alleviates heart oxidative damage and histopathological changes induced by TCDD which are in agreement with previous studies (2, 21). Abdulkareem and Nanakali (2020) indicated that QUE could improve oxidative stress and the expression of the *CYP1A1* gene caused by TCDD in liver and testis tissue (2, 3). Ciftci et al (2013) showed that QUE attenuated toxicity induced by TCDD in rat liver (21). Moreover, QUE could improve oxidative damage, histological changes and liver and kidney dysfunctions induced by paracetamol (29) and cadmium (30). Moreover, these findings and our results are supported by the previous reported results (2, 3). Furthermore, QUE can improve the adverse effects of TCDD by signaling pathways-mediated by AHR (2, 12). As previously mentioned, TCDD can interact with AHR as an agonist and mediates signaling pathways. Therefore, these two molecules, like the agonist and antagonist of this receptor, can create many biological effects that require further study. Improvement of oxidative factors after QUE consumption was supported by improved cardiac tissue damage. ROS overproduction can react with macromolecules such as lipids, proteins and nucleic acids, and lead to oxidative damage and tissue injury (31, 32). While QUE can protect these effects and suppressed TCDD-induced toxicity in heart and other tissue (21). Shin *et al.* (2007) also showed that nuclear factor erythroid 2-related factor 2 (Nrf2) modulates AHR signaling pathways in an exogenous ligand-independent manner (33). Nrf2 is an emerging regulator of cellular resistance to oxidants. Nrf2 controls the basal and induced expression of an array of antioxidant response element-dependent genes to regulate the physiological and pathophysiological outcomes of oxidant exposure (34). QUE could exert antagonistic activity against AHR in the liver (21). Therefore, it seems logical that QUE can improve oxidative damage and tissue structure of the heart by altering the expression of the Nrf2 gene that requires further study. However, there are other unknown mechanisms, such as inflammation and apoptosis that need further study. Much research has been done on cardiovascular disease (35-38), some reports have suggested that radiation is effective (39-

42). In this regard, the role of antioxidants is inevitable (43-44). The results of this study, if repeated and developed, may be effective in this regard.

To sum up, it can be concluded that QUE was able to improve the structure of the heart by inhibiting TCDD-induced oxidative damage.

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Conflict of interest

The authors state that there is no conflict of interest.

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