Research Article

Quercetin dihydrate ameliorates triton induced hyperlipidemia in rats

Neha Rani [1], Ajay Singh Kushwah [1*], Ghanshyam Das Gupta [2]

[1] *Department of Pharmacology, ASBASJSMemorial College of Pharmacy, Bela-140111, Ropar, (Punjab) India*

[2] *ISF College of Pharmacy, Moga-142001 (Punjab) India*

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Abstract

Background: Quercetin dihydrate is a dietary flavonoid bearing antioxidant, reduce the lipid peroxidation, antitumor, and anti-inflammatory potential, present in a broad range of fruits vegetables and beverages. **Objective:** The present study deals with evaluating the effect of quercetin dihydrate on triton induced hyperlipidemia in rats. **Materials and methods:** Adult Wistar rats (either sex) divided into five groups: Normal control, Triton control, the dose of quercetin dihydrate (25, 50mg/kg; p.o.) Atorvastatin (10mg/kg; p.o.) serve as standard drug administered to triton induced hyperlipidemic rats for 28 days. **Results:** The results significantly demonstrated in Triton induced hyperlipidemic rats, treatment with quercetin dihydrate reduced weight gain, lipid profile, liver function, lipid peroxidation, changes in aortic lesion were also observed after treatment. This finding indicates that quercetin dihydrate contains flavonoids able to lower plasma lipid concentrations, improve oral fat tolerance, HDL level and might be beneficial in the treatment of hyperlipidemia and atherosclerosis. **Conclusion:** support on the results of the present study shows that quercetin dihydrate protects from triton induced hyperlipidemia due to reducing blood lipid parameters, hemodynamic parameters, and increased antioxidant status.

Keywords: Hyperlipidemia, Triton X100, Quercetin dihydrate, Oral fat tolerance test

Introduction

Alteration in dietary pattern due to the modernization of societies includes high saturated fat intake along with low fiber content caused lipid dysfunction. Hyperlipidemia is a metabolic condition in which their abnormalities associated with high level of lipids (Siri et al., 2010). Well known risk factor for hypercholesterolemia in humans caused by obesity which elevates total cholesterol, low-density lipoprotein cholesterol (LDL-C) and decrease (HDL-C) (Pearson et al., 2002) and other important contributors that relates to this disease includes inflammation, oxidative stress and insulin resistance (Libby, 2000). The excess free radicals can create various cell dysfunctions, that are the primary risk factors for the initiation and formation of free radicals and oxidized LDL cholesterol contributes to the blockage of arteries which eventually leads to initiation and progression of atherosclerosis and heart attack (Irudayaraj et al., 2013). Current treatment of hyperlipidemia and reduces the risk for cardiovascular diseases by changing the lifestyle and food habits, intake nutraceuticals, low fiber diet, unsaturated fats. The most effective and widely used drugs for the treatment of hyperlipidemia are the statins (Adnan et al., 2011). Current available anti-hyperlipidemic drugs associated with various side effects like hepatotoxicity, hyperuricemia, and myositis. Quercetin dihydrate (3, 3, 4, 5, 7-Penta-hydroxy flavone) is a flavonoid or more specifically a subclass called flavonol which is widely distributed in the plant kingdom. It is found in many foods such as onions, cilantro, sweet potatoes, broccoli, and kale. Traditionally reported activity of quercetin dihydrate have anti-obesity (Rayalam et al., 2008; Ahn et al., 2008), antidiabetic (Di Carlo et al., 1999; vessel et al., 2003), antifertility (Formica et al., 1995), antiatherosclerotic effect (Salvamani et al., 2014; Kleemann et al., 2011). *In- vitro*, it has been shown that quercetin is strong antioxidant with peroxyl radical-scavenging activity and inhibits xanthine oxidase. The epidemiological studies and evidence have implicated the role of quercetin inhibit peroxynitrite radicals suppresses oxidation of low-density lipoprotein (LDL) in atherogenesis (Da Silva et al., 1998). It

Address for Corresponding Author:
Ajay Singh Kushwah
Assistant Professor
Department of Pharmacology
ASBASJS Memorial College of Pharmacy, Bela-140111, Ropar, (Punjab) India
Tele: +91-9417459195, FAX-01881-263655
E-mail: kushwah_ph05@yahoo.co.in

prevents endothelial dysfunction by enhancing the vasorelaxant process leading to a reduction of arterial pressure, arterial thrombus formation, and another cardiovascular disease.

However, no sufficient studies have been carried out to explore the role of quercetin dihydrate as in the treatment of hyperlipidemia in Triton induce model to best of our knowledge. Therefore, the present study aims at study to explore the effect of quercetin dihydrate on Triton induced hyperlipidemia in rats.

Material and methods

Drugs, Chemicals and Estimation kits

Quercetin dihydrate, Urethane, Triton x100, Oil red O was procured was procured from Hi-media Mumbai and Atorvastatin and olive oil purchased from local market. Cholesterol, SGPT, SGOT and TGs were analyzed with commercially available kits using autoanalyzer (Erba Diagnostics, Chandigarh and Span Diagnostics Ltd., Surat).

Experimental animals and housing conditions and ethical approval

Albino Wistar rats weighing 180-200g were procured from Central Animal House Facility, AIIMS, New Delhi. The animals were kept in quarantine section till monitoring of health status of animals and subsequently transferred to the housing area. The animals were acclimatized for seven days to the housing conditions of Central Animal House Facility of ASBASJSM College of Pharmacy, Bela prior to experiments. Animals were housed in polypropylene cages with dust free rice husk as a bedding material and maintained under standard laboratory conditions of temperature (23 ± 2°C), humidity (40 ± 10%) and 12:12 h dark/light cycles. The animals were fed with standard rodent pellet diet (Ashirwad Industries, Mohali) and water *ad-libitum*. The research protocol of this study had been approved by Institutional Animal Ethics Committee (IAEC) of ASBASJSM College of Pharmacy, BELA (Ropar) and void approval no. ASCB/IAEC/09/16/112, care of laboratory animals was done as per CPCSEA guidelines, Ministry of Forests & Environment and Government of India.

Induction of hyperlipidemia

Hyperlipidemia was induced in Wistar rats by intraperitoneal injection of freshly prepared Triton (100 mg/kg; i.p.) in water at 25ºC after overnight fasting for 18 h inducing hyperlipidemia in disease control, treatment and standard (Atorvastatin) group animals as per study plan (Adigun et al., 2016).

Experimental design

Overnight fasted rats were randomly divided into five groups of six animals of each group (n=6). Group I (NC): Normal control rats were received normal saline. Group II (TC): Triton control group were received Triton (100 mg/kg; i.p.), test group III and IV (T+ Quercetin dihydrate): received the low dose or high dose of Quercetin dihydrate (25 or 50 mg/kg; p.o.) Group V serves as a standard group (T+ ATORVA): were received atorvastatin (10 mg/kg; p.o.), study group II to V animals were administered Triton x100, except of group I, body weights of the study animals were measured routinely, end of the study (29th day), all overnight fasted animals were sacrificed by cervical dislocation and then blood samples were collected.

Assessment of hematological parameters

End of the study (29th day), blood sample were obtained from the rats by puncturing retro-orbital plexus using glass capillary tubes under chloroform anaesthesia and collected and plasma and serum was separated for analysis of different haematological parameters; total cholesterol (TC), HDL (high density lipoprotein), LDL (low density lipoprotein), VLDL (very low density lipoprotein), TG (triglycerides), ALP (alkaline phosphatase), SGPT (Serum glutamic pyruvic transaminase), SGOT (Serum glutamic oxaloacetic transaminase), OFTT (Oral fat tolerance test), all analysis was performed with commercially available kits.

Oral fat tolerance test (OFTT)

For oral fat tolerance tests, the rats were fasted overnight (16 h) in standard cages with *ad libitum* free access to water. Rats were administered 0.5 mL/100g of olive oil by orally and blood was collected at 0, 30, 60, 120 min after fat load for measurement of TG level.

Measurement of hemodynamic parameters

Rats were anesthetized with 25% urethane (1.5g/kg, i.p). Throughout the experimental protocol body, temp of the animals was maintained at 37 ºC. The neck was opened with a ventral midline incision to perform the tracheotomy. The left carotid artery was cannulated with the polyethylene tube (internal diameter 0.30mm; outer diameter 0.40 mm) attached to a three-way cannula. The cannula was heparinized (Heparin 300 IU/ml) and connected to POWER LAB 4/30 (AD Instruments, NSW, Australia) system using a pressure transducer for the measurement of systolic, diastolic, mean arterial pressures and heart rate.

Biochemical studies of rat heart

Animals were sacrificed by cervical dislocation and the heart tissues were removed, washed with the cold isotonic saline and dried with filter paper. After centrifugation, supernatant was used for analysis of antioxidant enzymes, GSH (Ellman et al., 1959) and TBARS (Ohkawa et al., 1979) level.

Aorta staining

Perivascular fat was removed from the outer wall of the aorta, and the aorta was stained with oil red O (ORO) as described (Nunnari et al., 1989). Rats from all groups were sacrificed by cervical dislocation and aorta was removed. The aorta was washed rapidly in cold water to remove excess blood. The aorta was placed in the 10% formalin solution for 10 minutes. Then it washed with phosphate buffer solution (PBS) pH 7.4 twice or thrice. The section was placed in the ORO for 15 minutes. Oil Red O stained deposits were measured using Image Pro plus Image analysis system.

Statistical analysis

The data were expressed as Mean ± SEM (n=6 in each group) were analyzed by one-way ANOVA followed by Turkey multiple comparison tests using Graph Pad Prism software package. A value of P<0.05 was considered to be significant.

Results

Effect of Quercetin dihydrate (QD) on body weight

Triton control group showed significantly (p<0.05) increased in body weight as compared to the normal control group. The body weight significantly (p<0.05) reduced in quercetin dihydrate (25, 50 mg/kg; p.o.) treated group and atorvastatin (10 mg/kg; p.o.) standard group as compared to Triton control group. High dose of quercetin dihydrate (50 mg/kg; p.o.) decreased the body weight significantly (p<0.05) as compared to the low dose of quercetin dihydrate (25 mg/kg; p.o.) (Table 1).

Table 1. Effect of Quercetin dihydrate on body weight

Groups	Initial weight	Final weight	Wt. gain (g)	% Change in Wt.
Normal Control	180.6± 0.34	219.9± 0.37	38.99± 0.18	121.7± 0.09
TC (100mg/kg)	181.8± 0.27 [a]	260.8± 0.33 [a]	79± 0.57 [a]	143.5± 0.37 [a]
T+ QD (25mg/kg)	182.7± 0.53 [b]	244.7± 0.40 [b]	62.02± 0.35 [b]	133.6± 0.34 [b]
T+ QD (50mg/kg)	181.7± 0.24 [b, c]	226.1± 0.35 [b,c]	44.11± 0.47 [b,c]	124.3± 0.27 [b,c]
T+ ATORVA (10mg/kg)	182.5± 0.21 [b]	225.6± 0.61 [b]	43.08± 0.47 [b]	123.6± 0.30 [b]

NC: *Normal control;* ***TC (100mg/kg):*** *Triton control (100 mg/kg; i.p.);* ***T+ QD (25mg/kg):*** *Triton+ quercetin dihydrate low dose (25 mg/kg; p.o.);* ***T+ QD (50mg/kg):*** *Triton + quercetin dihydrate high dose (50 mg/kg; p.o.);* ***T+ATORVA (10 mg/kg):*** *Triton+ atorvastatin (10 mg/kg; p.o.).*

Total duration of study was 28 days. Values are expressed as mean ± S.E.M (n=6). [a] (p< 0.05) *vs* normal control group; [b] (p< 0.05) *vs* triton control group; [c] (p< 0.05) *vs* low dose quercetin dihydrate (25 mg/kg) treatment group (One way ANOVA followed by Tukey's test).

Effect of Quercetin dihydrate (QD) on Lipid profile and liver function test

Triton control group showed increased significantly (p<0.05) in lipid profile and liver function test (Cholesterol, LDL, VLDL, TG, ALP, SGOT and SGPT), except significantly (p<0.05) reduction in HDL level compared to the normal control group. Quercetin dihydrate (25, 50 mg/kg; p.o.) treated group and atorvastatin (10 mg/kg; p.o.) standard group decrease significantly (p<0.05) Cholesterol, LDL, VLDL, TG, ALP, SGOT and SGPT level as compared to Triton control group but these similar study group significantly (p<0.05) increase in HDL level compared to the normal control group. High dose of quercetin dihydrate (50 mg/kg; p.o.) compare vs. low dose of quercetin dihydrate (25mg/kg; p.o.) significantly (p<0.05) elevated the HDL level and significantly (p<0.05) decreased lipid profile and ALP, SGOT and SGPT level (Table 2).

Table 2. Effect of Quercetin dihydrate on various lipid parameters and liver function test

Groups	Normal control	TC (100mg/kg)	T+ QD (25mg/kg)	T+ QD (50mg/kg)	T+ ATORVA (10mg/kg)
Cholesterol	170.5±	256.3±	235±	214±	204.08±
(mg/dl)	2.88	3.75[a]	1.97[b]	1.34[b,c]	1.20[b]
HDL	58.39±	27.0±	42.07±	51.79±	56.4±
(mg/dl)	1.17	2.48[a]	0.74[b]	0.60[b,c]	0.43[b]
LDL	82.76±	166±	136.5±	128.39±	120.8±
(mg/dl)	5.07	2.78[a]	1.84[b]	1.45[b,c]	1.15[b]
VLDL	25.32±	63.29±	56.41±	27.29±	25.66±
(mg/dl)	0.30	0.70[a]	0.75[b]	0.35[b,c]	0.27[b]
TG	126.6±	316.5±	282.0±	136.4±	128.1±
(mg/dl)	1.54	3.54[a]	3.76[b]	1.77[b,c]	1.37[b]
ALP	118.8±	185.6±	163.5±	152.3±	148.7±
(IU/L)	1.71	1.28[a]	0.74[b]	0.77[b,c]	0.52[b]
SGOT	30.11±	109.3±	85.38±	72.22±	69.64±
(IU/L)	2.13	2.91[a]	1.43[b]	1.43[b,c]	0.60[b]
SGPT	35.42±	84.81±	73.98±	67.92±	64.8±
(IU/L)	2.19	0.26[a]	0.24[b]	0.65[b,c]	0.52[b]

NC: *Normal control;* ***TC (100mg/kg):*** *Triton control (100 mg/kg; i.p.);* ***T+ QD (25mg/kg):*** *Triton+ quercetin dihydrate low dose (25 mg/kg; p.o.);* ***T+ QD (50mg/kg):*** *Triton + quercetin dihydrate high dose (50 mg/kg; p.o.);* ***T+ATORVA (10 mg/kg):*** *Triton+ atorvastatin (10 mg/kg; p.o.).*

Total duration of study was 28 days. Values are expressed as mean ± S.E.M (n=6). [a] (p< 0.05) *vs* normal control group; [b] (p< 0.05) *vs* triton control group; [c] (p< 0.05) *vs* low dose quercetin dihydrate (25 mg/kg) treatment group (One way ANOVA followed by Tukey's test)

Effect of Quercetin dihydrate (QD) on Oral fat tolerance test (OFTT)

Rats were administered 0.5 mL/100g of olive oil by orally and blood samples were collected at 0, 30, 60, 120 min after fat load for measurement of TG level. Triton control group showed significantly (p<0.05) increased in TG level compared to the normal group. TGs level significantly (p<0.05) decreased in quercetin dihydrate (25, 50 mg/kg; p.o.) treated group and atorvastatin (10 mg/kg; p.o.) standard group as compared to Triton control group. High dose of quercetin dihydrate (50 mg/kg; p.o.) significantly (p<0.05) decreased TGs as compared to the low dose of quercetin dihydrate (25 mg/ kg; p.o.) (Figure 1).

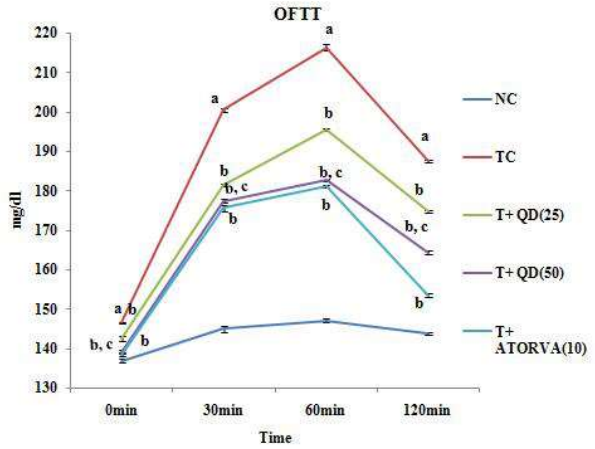

Figure 1. Effect of Quercetin dihydrate on Oral Fat Tolerance Test (OFTT). ***NC:*** *Normal control;* ***TC (100mg/kg):*** *Triton control (100 mg/kg; i.p.);* ***T+ QD (25mg/kg):*** *Triton+ quercetin dihydrate low dose (25 mg/kg; p.o.);* ***T+ QD (50mg/kg):*** *Triton + quercetin dihydrate high dose (50 mg/kg; p.o.);* ***T+ATORVA (10 mg/kg):*** *Triton+ atorvastatin (10 mg/kg; p.o.).*

Total duration of study was 28 days. Values are expressed as mean ± S.E.M (n=6). [a] ($p< 0.05$) *vs* normal control group; [b] ($p< 0.05$) *vs* triton control group; [c] ($p< 0.05$) *vs* low dose quercetin dihydrate (25 mg/kg) treatment group (One way ANOVA followed by Tukey's test).

Effect of Quercetin dihydrate (QD) on Hemodynamic parameters

Triton control group showed highly significant ($p<0.05$) increased in Heart rate (HR) SAP, DAP and decreased significant ($p<0.05$) the AP and MAP level as compared to the normal control group. HR, SAP, DAP level significant ($p<0.05$) reduced and increased significant ($p<0.05$) the AP, MAP level in quercetin dihydrate (25, 50 mg/kg; p.o.) treated group and atorvastatin (10 mg/kg; p.o.) standard group as compared to Triton control group. High dose of quercetin dihydrate (50 mg/kg; p.o.) decreased significantly ($p<0.05$) the HR, SAP, DAP and increased significant ($p<0.05$) the AP, MAP as compared to low dose of quercetin dihydrate (25 mg/kg; p.o.) (Table 3).

Table 3. Effect of Quercetin dihydrate on hemodynamic parameters

Groups	AP (mmHg)	HR (BPM)	MAP (mmHg)	SAP (mmHg)	DAP (mmHg)
Normal Control	122.6± 1.53	367.1± 2.03	123.7± 0.79	121.7± 0.31	83.72± 0.79
TC (100mg/kg)	91.49± 1.95[a]	461.0± 3.52[a]	93.89± 1.52 [a]	141.1± 0.35[a]	110± 1.87[a]
T+ QD (25mg/kg)	105.9± 1.73[b]	413.7± 3.43[b]	113.8± 1.38 [b]	133.4± 0.31 [b]	95.80± 0.51[b]
T+ QD (50mg/kg)	119.4± 0.34[b,c]	384.9± 3.24[b,c]	121± 0.69[b,c]	124.1± 1.07 [b, c]	88.22± 0.71[b,c]
T+ATORVA (10mg/kg)	124.5± 1.40[b]	377.1± 2.19[b]	123.9± 0.37[b]	122.5± 0.80 [b]	84.90± 0.38[b]

NC: *Normal control;* ***TC (100mg/kg):*** *Triton control (100 mg/kg; i.p.);* ***T+ QD (25mg/kg):*** *Triton+ quercetin dihydrate low dose (25 mg/kg; p.o.);* ***T+ QD (50mg/kg):*** *Triton + quercetin dihydrate high dose (50 mg/kg; p.o.);* ***T+ ATORVA (10 mg/kg):*** *Triton+ atorvastatin (10 mg/kg; p.o.).*

Total duration of study was 28 days. Values are expressed as mean ± S.E.M (n=6). [a] ($p< 0.05$) *vs* normal control group; [b] ($p< 0.05$) *vs* triton control group; [c] ($p< 0.05$) *vs* low dose quercetin dihydrate (25 mg/kg) treatment group (One way ANOVA followed by Tukey's test).

Effect of Quercetin dihydrate (QD) on antioxidant parameter in tissue (rat heart)

Triton control group showed highly significant ($p<0.05$) increased in lipid peroxidation (LPO) level and decrease significant ($p<0.05$) GSH level as compared to the normal control group. LPO level reduced significant ($p<0.05$) and increased significant ($p<0.05$) GSH in quercetin dihydrate (25, 50 mg/kg; p.o.) treated group and atorvastatin (10 mg/kg; p.o.) standard group as compared to Triton control group. High dose of quercetin dihydrate (50 mg/kg; p.o.) significant ($p<0.05$) decreased the LPO level significantly and increased significant ($p<0.05$) GSH as compared to the low dose of quercetin dihydrate (25 mg/kg; p.o.) (Table 4).

Table 4. Effect of Quercetin dihydrate on antioxidant (Lipid per oxidation) parameters

Groups	MDA	GSH
Normal control	53.09 ± 1.42	152.9 ± 0.82
TC(100mg/kg)	87.49± 1.39 [a]	40.52 ± 0.67 [a]
T+ QD(25mg/kg)	72.82± 0.90 [b]	74.81 ± 0.63 [b]
T+ QD(50mg/kg)	63.36± 0.69 [b, c]	103.5± 1.17 [b, c]
T+ ATORVA(10mg/kg)	59.99 ± 1.25 [b]	107.4± 1.18 [b]

NC: *Normal control;* ***TC (100mg/kg):*** *Triton control (100 mg/kg; i.p.);* ***T+ QD (25mg/kg):*** *Triton+ quercetin dihydrate low dose (25 mg/kg; p.o.);* ***T+ QD (50mg/kg):*** *Triton + quercetin dihydrate high dose (50 mg/kg; p.o.);* ***T+ATORVA (10 mg/kg):*** *Triton+ atorvastatin (10 mg/kg; p.o.).*

Total duration of study was 28 days. Values are expressed as mean ± S.E.M (n=6). [a] ($p< 0.05$) *vs* normal control group; [b] ($p< 0.05$) *vs* triton control group; [c] ($p< 0.05$) *vs* low dose quercetin dihydrate (25 mg/kg) treatment group (One way ANOVA followed by Tukey's test).

Aorta staining

The percentage of aortic lesions was highly significant ($p<0.05$) in TC control group when compared to normal control group. The aortic lesions percentage decreased significant ($p<0.05$) in Atorvastatin (10 mg/kg; p.o.) and moderately decreased significant ($p<0.05$) by Quercetin dihydrate (25, 50 mg/kg; p.o.) treated group when compared to TC group (Table 5 and Figure 2).

Discussion

Abnormal level of plasma lipid parameters resulting from unhealthy food, sedentary life style and deficiency in regulatory hormone leads to the various metabolic abnormalities observed in hyperlipidemia which causes damage, dysfunction, and failure of various organs (Olaitan

et al., 2012). According to the oxidation hypothesis (Steinberg and Witztum, 2010) proposed that LDL, in its oxidized form, is crucial to cellular uptake to form macrophages derived from cells in the early development of atherosclerotic lesions. Oxidized LDL has many atherogenic leads to the formation of foam cells and initiates endothelial damage. The accumulation of oxidative modified LDL in the arterial wall, promoting endothelial dysfunction and development of atherosclerosis and congestive heart disease (Castilla et al., 2009). Currently available drugs have limited often used due to a number of side effects. The consumption of synthetic drugs leads several side effects and abnormal liver function (Sudha et al., 2011). There are many reports that support modulations of oxidative stress through treatment with antioxidants can effectively reduce lipid levels (Evans et al., 2002).

Table 5. Effect of Quercetin dihydrate on aortic lesions in percentage

Groups	Aortic Lesion %
NC	2.69
TC	14.42 [a]
T+ QD(25mg/kg)	12.36 [b]
T+ QD(50mg/kg)	11.6 [b, c]
T+ ATORVA(10mg/kg)	9.72 [b]

NC: *Normal control;* ***TC (100mg/kg):*** *Triton control (100 mg/kg; i.p.);* ***T+ QD (25mg/kg):*** *Triton+ quercetin dihydrate low dose (25 mg/kg; p.o.);* ***T+ QD (50mg/kg):*** *Triton + quercetin dihydrate high dose (50 mg/kg; p.o.);* ***T+ ATORVA (10 mg/kg):*** *Triton+ atorvastatin (10 mg/kg; p.o.).*

Total duration of study was 28 days. Values are expressed as mean ± S.E.M (n=6). [a] ($p< 0.05$) *vs* normal control group; [b] ($p< 0.05$) *vs* triton control group; [c] ($p< 0.05$) *vs* low dose quercetin dihydrate (25 mg/kg) treatment group (One way ANOVA followed by Tukey's test).

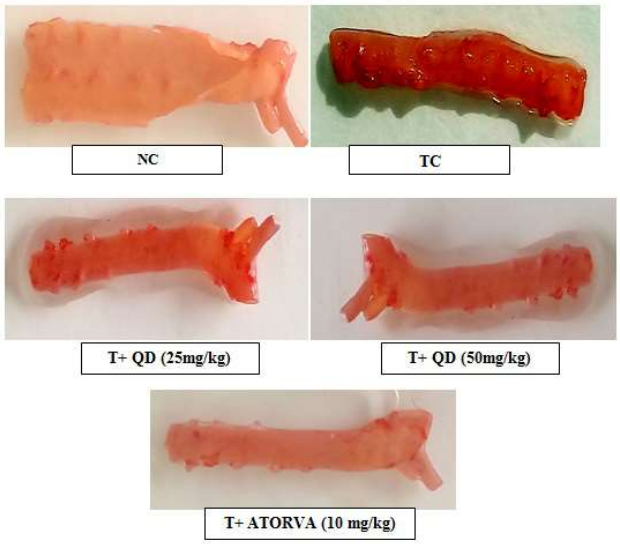

Figure 2. Effect of Quercetin dihydrate on aortic lesion

Quercetin dihydrate the main representative of the flavonols and phenolic acid, is found in plants and foodstuffs as derivatives such as cinnamic and benzoic acid, catechins, procyanidins and condensed tannins. Flavonoids are widely distributed among various plants and in numerous studies have shown that quercetin has antioxidant, antiasthmatic, antiatherosclerotic and diabetic complications (Rogerio et al., 2008; Garelnabi et al., 2011; Lamson et al., 2000). Quercetin is a strong antioxidant with peroxyl radical-scavenging activity (Ioku et al., 1995) and suppresses oxidation of low-density lipoprotein (Safari and Sheikh, 2003; Kerry and Abbey, 1997). Hyperlipidemia is not only secondary metabolic dysregulations associated with diabetes (Chattopadhyay et al., 2005). Obesity can increase the burden on the heart with deteriorating coronary circulation and atherogenesis. Increase inbody weight and fat deposition is the chief indicators for the gradual progress of obesity (Kumar et al., 2010). In our findings administration of Triton shows significant increases in the body weight as compared with normal control group. Body weight reduced in atorvastatin (10 mg/kg) standard group and quercetin dihydrate (25 and 50 mg/kg) respectively as compared to Triton control group.

Hyperlipidemia is the leading risk factor for atherosclerosis. Epidemiological studies have been reported that raise the concentration of total cholesterol or LDL–cholesterol in plasma with increased incidence of atherosclerotic events. It has further indicated that the clinical complications of hyperlipidemia could be suppressed and life prolonged when plasma lipids are lowered by antihyperlipidemic agents (Musunuru, 2010). Various models to induce hyperlipidemia include; Cholesterol, fructose and high-fat diet, cyclosporine, thiazides, alcohol, smoking . Triton X-100 has successfully been used to induce hyperlipidemia in rats in previous studies and it was chosen as the hyperlipidemic model due to its convenience, reproducibility, and availability (Ghule et al., 2006). Triton a non-ionic detergent inhibits the catabolising enzymes lipoprotein lipase (LPL) and lecithin cholesterol acetyl transferase (LCAT) by blocking the uptake of lipoprotein from the circulation by extra hepatic tissues, which cause an increase in the level of circulatory lipoproteins (Surya et al., 2016). It alters VLDL-C, rendering them refractive to the action of lipolytic enzymes of blood and tissue. This prevents or delays their removal from blood and secondarily stimulates the hepatic cholesterol biosynthesis, thus enhancing hyperlipidemia (Goldfarb et al. 1978). Study result in the level of different lipids like cholesterol, LDL, VLDL increases in the blood stream and they cause endothelial dysfunctioning (Sikarwar et al., 2012).

Quercetin has normalized the up regulated lipoprotein levels in plasma through their antilipo-peroxidative and

antioxidant actions, which inhibit the extensive accumulation of cholesterol and oxidized lipid components as well as prevent hypercholesterolemia (Fuhrman and Aviram, 2001). Triton has the ability to increase in the lipid profile level. In our findings administration of Triton significantly increase the level of lipids such as total cholesterol, LDL, (VLDL), TG and decrease the level of HDL in the Triton control group when compared to normal control group. Oral administration of atorvastatin (10 mg/kg) decrease total cholesterol, LDL, VLDL, TG and increase the level of HDL when compared with Triton control group. After 28 days treatment with quercetin dihydrate (25 and 50mg/kg) show the significant decrease in total cholesterol, LDL, VLDL, TG and increase the level of HDL with respect to both doses of quercetin dihydrate when compared to Triton control group. These suggested that treatment with quercetin dihydrate lower the lipid level.

Elevated levels of fasting triacylglycerol (TAG) are associated with increased risk for atherosclerosis (Patel et al., 2004; Gotto, 1998; Talayero and Sacks, 2011). Accumulated evidence suggests that postprandial lipemia is an atherogenic process, causing oxidative stress, inflammation and unfavorable alternations in lipoproteins (Patsch et al., 2000; Alipour et al., 2008). Several factors and circumstances may influence postprandial lipemia, including obesity, fasting hyper triglyceridemiamia and energy deficit (Maraki and Sidosis, 2010; Lopez et al., 2007). The cardiovascular protective properties of quercetin might, therefore, be explained by the lipid lowering effect of quercetin (Boden, 2008). Postprandial lipemia is assessed using the oral fat tolerance test (OFTT). Oral fat tolerance test performed immediately after the rats fasted overnight. Triton control group, increase TAG level at 30min, 60min, and 120min as compared with normal control group.

The liver enzymes are normally found in circulation in small amounts because of hepatic growth and repair. SGOT and SGPT activities were elevated in hypercholesterolemia (Sudhahar et al., 2007). Quercetin is the regulator of fatty acid oxidation in the liver; it abolished hepatic steatosis, prevented the infiltration of inflammatory cells in the liver, and reduced the portal fibrosis along with improvements in liver function due to their hepatoprotective action (Panchal et al., 2012). Triton has the ability to destruct endothelial cells by lipid peroxidation. As a result, this, cytosolic enzymes ALP, SGOT and SGPT are released into the blood stream and serve as the diagnostic markers of hepatotoxicity and myocardial tissue damage. In our findings administration of Triton significantly increase the level the diagnostic marker such as ALP, SGOT, and SGPT (45.9, 58.8 and 64.3%) respectively when compared to normal control group. During oral administration of atorvastatin (10 mg/kg) ALP, SGOT and SGPT level significantly decrease (33.3, 36 and 46.7%) when compared to Triton control group. The ALP, SGOT and SGPT level significantly decreases in quercetin dihydrate (25 and 50 mg/kg) in treated group with respect to various cytosolic enzyme levels when compared to Triton control group. These suggested that treatment with quercetin dihydrate prevent the release of these enzymes due to its antioxidant activity.

Hyperlipidemia, a strong forecaster of cardiovascular disease, causes endothelial damage and the defeat of physiological vasomotor action that results from endothelial injury may turn out to be manifested as amplified hypertension (Nickenig, 2002; Anderson et al., 1987; Dalal et al., 2012). Quercetin has been reported to improve endothelium-dependent vasorelaxation in aorta, decreases systolic blood pressure and reduces cardiac hypertrophy and proteinuria in hypertensive rats, enhancement of endothelial nitric oxide synthase (eNOS) activity and reduction of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase in hypertensive rats (Garcia et al., 2005; Sanchez et al., 2006). In the present investigation, administration of Triton show the significant decrease in the AP, MAP, but increase in the SAP, DAP and HR in the heart was observed when compared to normal control group. Treatment with QD (25 and 50 mg/kg; p.o.) shows the significant elevation in the AP, MAP respectively, but the reduction in SAP, DAP, and HR with respect to dose, when compared with Triton control group. Treatment with atorvastatin (10 mg/kg) for a period of 28 days shows the significant elevation in the AP, MAP but the reduction in SAP, DAP, and HR in the heart when compared to TC group.

Oxygen free radicals or reactive oxygen species (ROS) are the products of normal metabolic and signal-transduction events within a cell (Prasad, 2008). These oxygen-derived radicals inactive both enzymic and non-enzymic antioxidant system leading to oxidative stress and cellular damage (Ajiboye et al., 2013) and free radical oxidation is responsible for the degradation of fatty acids and their esters in biological membranes and lipoproteins (Morgan et al., 2007). GSH has a direct antioxidant function by reacting with super oxide radicals and singlet oxygen followed by the formation of oxidized GSH and other disulfides (Iton et al., 1999 and Magdalena et al., 2008). Similarly, depletion in the level of GSH in hyperlipidemic conditions has been reported to be due to the oxidation of electrophilic compounds. This depletion would invariably lead to increase in glutathione disulfide (GSSG), as this is the product of GSH oxidation (Wolin, 2000). Quercetin partially protected blood glutathione, suppressed nitric oxide metabolites and superoxide anion production (Luangaram et al., 2007). In the present investigation, administration of Triton significantly reduced GSH, when

compared to normal control group. Oral administration of atorvastatin (10 mg/kg) for a period of 28 days show a significant increase the level of GSH when compared to TC group. QD (25& 50 mg/kg) treated group showed a significant elevation in the level of GSH respectively when compared with Triton control group. Many oxygenated compounds, particular aldehydes such as malondialdehyde (MDA) and conjugated dienes, are produced during the attack of free radicals to membrane lipoproteins and polyunsaturated fatty acids (Ryun and Bae, 2014). The increased in malondialdehyde is in consonance with suggesting inactive antioxidant system (Vijayaraj et al., 2013). This could deform membrane organization and induces functional loss of membrane (Niki, 2009). Lipid peroxidation has been previously established in Triton induced hyperlipidemic rats by assessing the level of malondialdehyde (Minhajuddin et al., 2005). The antioxidant properties of quercetin might be due to its capability to chelate transition metal ions and prevents oxidative hassle by scavenging superoxide anions, reduced the activities of the cardiac enzymes in the serum. This may be mainly due to the anti-lipoperoxidation, antioxidant and membrane stabilizing properties of quercetin (Devi et al., 2010). In the present investigation, administration of Triton shows the significant elevation in the level of LPO (46.5%), when compared to normal control group. Oral administration of atorvastatin (10 mg/kg) for 28 study periods shows a significant decrease in the level of LPO when compared to TC group. Treatments with quercetin dihydrate (25 and 50 mg/kg. p.o.) treated group significantly decrease the level of LPO respectively in both groups was observed when compared with Triton control group. Oil Red O is a lysochrome (fat soluble) diazo dye which is used for staining of triglycerides and lipids. It mainly targeted the fat deposits on the surface the tissue (Nunnari et al., 1989). Experimental observations show an increase in aortic lesions in TC group which reduced in Atorvastatin (10 mg/kg) and quercetin dihydrate (25, 50 mg/kg) treated group respectively. This data shows that quercetin dihydrate is capable of limiting the aortic lesions. Therefore, the present study suggests a protective effect of quercetin dihydrate on Triton induced hyperlipidemia in rats. The drug quercetin dihydrate has an antioxidant activity due to the ability to scavenge free radicals produced by Triton and improve the activity of lipid profile, cardiac marker and antioxidant decreased the lipid peroxidation in quercetin treated rats. All these estimations biochemical, hemodynamic, aorta staining have shown that 50 mg/kg dose of the drug quercetin dihydrate) is better effective than 25 mg/kg. A Higher dose of quercetin dihydrate (50 mg/kg) has also shown slightly different results as compared to atorvastatin (standard drug).

Conflict of interest

We declare that we have no conflict of interest.

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