Protective Effect of Quercetin on Atrazine-Induced Oxidative Stress in the Liver, Kidney, Brain, and Heart of Adult Wistar Rats

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ABSTRACT

Background: The conflicting roles of quercetin against tissue pathologies associated with oxidative stress are known. Objective: To evaluate the effect of quercetin at doses of 5 mg/kg (Q5) or 10 mg/kg (Q10) against atrazine (120 mg/kg, ATZ)-induced oxidative stress in various tissues of rats. Materials and Methods: Adult male albino Wistar rats were administered ATZ, Q5, and Q10 alone or in combination for 16 days. At the end of the 16th day, the animals were sacrificed by cervical dislocation; and the blood, heart, brain, kidney and liver were collected and used for biochemical determinations and histopathological examination. Results: Q10 but not Q5 attenuated ATZ-induced increase in the levels of serum enzyme markers sorbitol dehydrogenase (SDH), acid phosphatase (ACP), alkaline phosphatase (ALP), and aspartate aminotransferase (AST). The heart was less susceptible to ATZ-induced oxidative stress than the liver, kidney, and brain of treated animals, and there were tendencies for synergistic effects in the heart and liver of Q5 + ATZ-treated rats. Oxidative stress-induced by ATZ in terms of increased lipid peroxidation level and superoxide dismutase (SOD) activity was decreased in the brain of the Q5 + ATZ-treated rats but not that of the Q10 + ATZ-treated rats. Conversely, histopathological changes and oxidative stress-induced by ATZ in terms of elevated lipid peroxidation level, decreased SOD, and catalase (CAT) activities were prevented in the kidney and liver of the Q10 + ATZ-treated rats but not that of the Q5 + ATZ-treated rats. Conclusion: Quercetin at the investigated doses and especially the low dose may not protect against ATZ-induced oxidative stress in rat tissues in an overall sense.

Key words: Atrazine, malondialdehyde, oxidative stress, quercetin, serum marker enzymes

INTRODUCTION

More attention has been paid to the protective effects of flavonoids against drug-induced toxicities especially whenever oxidative stress is involved.[1] Quercetin, a representative flavonoid shows a variety of biological activities, including anticarcinogenic, antiinflammatory, and antiviral actions. The protective effects of quercetin against chemically induced tissue pathologies are widely known. For example, quercetin protects carbon tetrachloride-induced hepatotoxicity, 2,4-D-induced oxidative damage in spermatogonial cells, ethanol-induced oxidative stress, cyclosporin-induced nephrotoxicity, cisplatin-induced cytotoxicity in cultured tubular epithelial cells, atrazine (ATZ)-induced cytotoxicity in cultured Sertoli-germ cells and Leydig cells.[2-8] Many of these beneficial effects of quercetin are considered to be related to the experimental situation, antioxidant properties of quercetin, and the dose of quercetin used.[9] For instance, quercetin inhibits the deoxyribonucleic acid (DNA) damage caused by H₂O₂, but at high concentration it induces cellular DNA damage,[7] and also act as pro-oxidants on glutathione antioxidant system.[9-11] ATZ, a triazine-based herbicide extensively used in agriculture worldwide, is a well-known environmental
Abarikwu: Toxicity in rats by the combine effects of ATZ and QT

pollutant that is reported to induce toxic effects in several tissues of mammalian experimental models.\cite{12} It is known to cause hepatic damage in rats and pigs\cite{13-15} disrupt the functioning of the reproductive tissues\cite{16-18} cause DNA damage and genotoxicity in the stomach, kidney, and liver of rats;\cite{19,20} damage rat erythrocytes\cite{21} as well as induce oxidative stress in several experimental models.\cite{8,21-23} We previously reported that ATZ at a dose of 120 mg/kg induces oxidative stress in rat tissues and blood at 16 days of treatment, and that the oxidative stress was associated with increased lipid peroxidation and changes in the antioxidative system.\cite{22,23} Data from our laboratories have also revealed that experimental models involving co-treatment of 120 mg/kg ATZ and 20 mg/kg quercetin resulted in increased susceptibility of hepatic tissues and reproductive organs including the testis and epididymides to ATZ-induced oxidative damage and tissue pathologies\cite{22,24} even when there was no toxicity associated with quercetin at the investigated dose,\cite{24,25} suggesting that the protective effect of quercetin in this experimental model depends on the dose of quercetin that interacted with ATZ. Because quercetin is widely distributed in many fruit, vegetables, and many other dietary sources, highly consumed by humans either as supplement or directly from natural sources, and have both pro-oxidant and antioxidant nature,\cite{24} information on its appropriate dose that could be beneficial in ATZ-induced tissue pathogenesis is significant. Therefore, the present studies were initiated with lower doses of quercetin (5 mg/kg and 10 mg/kg) with the intention of selecting appropriate dose of quercetin that can protect against ATZ-induced cardio-hepatoarenal and brain-oxidative damage.

MATERIALS AND METHODS

Thirty-six adult male rats (Wistar albino) with an average weight of 164 ± 7.38 gm were provided by the animal house of the Department of Biochemistry, University of Ibadan, Nigeria and housed in six groups each containing six animals. The animals were maintained under 12 light: 12 dark cycle and were supplied with water and feed ad libitum. The rats were housed for a minimum of 1 week to acclimatize before being dosed with the test substances. The experimental designs and protocols for study were in accordance with the standard guide for the care and use of laboratory animals. ATZ in the commercial product cotrazine 80WP (an 80% wettable powder) were obtained from Nantong foreign trade, Meheco, China. Quercetin was obtained from Sigma Chemicals (St. Louis, MO). All other reagents were commercially available analytical-grade chemicals. The Q5 and Q10 groups were orally administered 5 mg/kg and 10 mg/kg quercetin (QT), respectively, ATZ was dissolved in the vehicle (corn oil) and orally administered to the ATZ groups at a dose equivalent to 120 mg/kg body weight (based on the active ingredient). QT was simultaneously administered with ATZ in the Q5 + ATZ groups and Q10 + ATZ groups at the same dose of QT and ATZ in the other groups. The control groups was administered the vehicle (2 mL/kg body weight) and all the treatment continued for 16 days. A 16-day period was chosen because we established that this is the minimum period required for ATZ to cause changes in the antioxidative system in rats and consequently induce oxidative damage.\cite{22,23} At the end of the 16th day of treatment, the rats in each group were sacrificed, and the heart, liver, brain, and kidney of each rat were quickly excised, cleared of adhering fat, rinsed with a cold 1.15% potassium chloride, and weighed. One kidney, portion of the liver, cerebrum, and cerebellum of each rat were preserved in neutral buffered formalin. Tissues were sectioned and stained routinely with hematoxylin and cosin for microscopy. The tissues were homogenized using Potter-Elvehjem homogenizer in a 4 volume of 50 mM Tris-HCl buffer (pH 7.4) containing 1.15% potassium chloride and centrifuged at 10,000× g, 4°C for 10 min. The supernatant was used for the measurement of the biochemical markers of oxidative stress. The activity of superoxide dismutase (SOD) was assayed by the method described by Misra and Fridovich\cite{26} and expressed as units/mg protein. The catalase (CA) T activity was assayed by the method of Sinha\cite{27} and expressed as expressed as µmol H₂O₂ consumed/min. The level of reduced glutathione (GSH) was determined at 412 nm using the method described by Sedlak and Lindsay\cite{28} and was expressed as µg GSH/mg protein. Lipid peroxidation was quantified as malondialdehyde (MDA) according to the method described by Ohkawa et al.,\cite{29} and expressed as µmol MDA/g tissue. Protein concentration was determined by the method of Lowry et al.,\cite{30} Blood collected through an eye vein was transferred into non-heparinized tubes for the recovery of serum. The serum was processed for the measurement of acid phosphatase (ACP)\cite{31} and alkaline phosphatase (ALP)\cite{32} using p-nitrophenylphosphate (PNPP) as the substrate. The aspartate aminotransferase (AST) activity was estimated by the method of Reitman and Frankel.\cite{33} The sorbitol dehydrogenase (SDH) assay was based on the conversion of sorbitol to fructose.\cite{34} The appearance of nicotinamide adenine dinucleotide (NADH) was measured spectrophotometrically at 340 nm. Data were expressed as mean ± standard deviation (SD), and the statistical analysis was performed with the Statistical Package for the Social Sciences (SPSS) Statistics 17.0 (SPSS Inc., Chicago, IL, USA). All the statistical analyses were analyzed by analysis of variance (ANOVA) followed by Dunnett’s test as a post hoc test. P values less than 0.05 were considered to indicate statistical significance.

RESULTS AND DISCUSSION

The rats in the group of ATZ + Q5 showed some clinical signs such as lethargy, weight loss [Table 1] leading
finally to the death of 1 animal at day 9. The animals in the other groups remained relatively in good health throughout the study and there were no exposure-related clinical observations. The effects of ATZ administration on tissue-damages index were evaluated as marker enzymes in serum samples from control and treated rats. The results showed that ATZ caused an increase in ALP, ACP, AST, and SDH. Co-administration of Q5 had no effect on ATZ-induced changes on these marker enzymes. In the Q10 + ATZ animals, the changes caused by ATZ on the serum-marker enzymes were normalised to near the control values. Q5 or Q10 alone has no effect on the serum-marker enzymes [Figure 1]. ATZ treatment caused a marked effect on MDA concentration and the key constituent of antioxidative defense system [Table 2]. According to our results, MDA level significantly increased in the brain, liver, and kidney but no alterations were observed in the heart. SOD activity significantly increased in the brain, whereas it decreased in the kidney and liver but did not change in the heart. Catalase (CAT) activity significantly decreased in the brain, liver, and kidney without significant change in the heart. Meanwhile GSH levels remain unchanged in all the tissues of rats treated with ATZ except in the liver where the level was increased. Treatments with Q5 reversed SOD activity in the brain but not in the kidney and liver, and have synergistic effects in the heart. MDA values were normalized in the brain but not in the kidney, whereas MDA levels in the heart remain unaltered in these groups of animals. Furthermore, the combine administration of Q5 + ATZ demonstrated synergistic effects on MDA level in the liver. GSH levels remain unaltered in the brain, kidney, and heart except in the liver where its level remains high. In addition, the CAT activity in the brain and kidney of the Q5 + ATZ animals remain low, and were decreased in the liver and heart comparable to the ATZ-treated rats. Treatment with Q10 could not prevent ATZ-induced increase in the MDA level in the brain, but it decreased the MDA value in the kidney and liver when compared to the ATZ value. Furthermore, the MDA level in the kidney and liver was lower in the Q10 + ATZ group than in the Q5 + ATZ animals. SOD activity was normalized to the control value in the kidney, liver, and heart of Q10 + ATZ animals except in the brain where its activity was still high compared to the control value but was decreased compared to the ATZ value [Table 2], suggesting that Q10 was not as effective in restoring to normalcy of the SOD activity in the brain than in the other tissues. Thus, the application of this dose of QT (10 mg/kg body weight) could potentially inhibit oxidative stress in the kidney and liver but not the brain of the ATZ-treated

**Table 1: Effects of atrazine and quercetin on body weights of rats**

| Variables | Control | Q5 | Q10 | ATZ | Q5 + ATZ | Q10 + ATZ |
|-----------|---------|----|-----|-----|---------|----------|
| Body weight (g) |         |    |     |     |         |          |
| Beginning | 156±229 | 166±319 | 172±279 | 166±269 | 170±359 | 154±199  |
| Finally   | 180±239 | 206±339 | 190±349 | 168±299 | 139±349 | 157±359  |

n=5. Values P<0.05).

**Table 2: Effects of ATZ and quercetin on antioxidant defense systems and MDA levels in various tissues of rats**

| Variables | Control | Q5 | Q10 | ATZ | Q5 + ATZ | Q10 + ATZ |
|-----------|---------|----|-----|-----|---------|----------|
| Brain     |         |    |     |     |         |          |
| SOD       | 56±219  | 61±239 | 79±259 | 117±239 | 59±249  | 83±259   |
| MDA       | 28±1.79 | 27±1.89 | 71±1.59 | 68±1.29 | 28±4.29 | 62±3.39  |
| GSH       | 13±0.79 | 13±0.69 | 13±0.69 | 13±0.79 | 13±0.89 | 13±0.59  |
| CAT       | 54±5.19 | 53±5.29 | 51±4.19 | 43±4.03 | 41±6.59 | 50±8.39  |
| Kidney    |         |    |     |     |         |          |
| SOD       | 70±11.19 | 64±811 | 78±19.21 | 28±11.89 | 31±14.9 | 61±12.9  |
| MDA       | 41±3.09 | 43±2.19 | 41±3.69 | 59±6.29 | 63±2.59 | 53±3.19  |
| GSH       | 2±0.59  | 2±0.49 | 2±0.49 | 2±0.49 | 2±0.49  | 2±0.49   |
| CAT       | 140±199 | 134±179 | 137±199 | 85±209 | 67±14.9 | 132±179  |
| Liver     |         |    |     |     |         |          |
| SOD       | 84±11.89 | 85±12.29 | 81±12.59 | 60±129 | 42±109  | 78±11.39 |
| MDA       | 66±4.79 | 59±5.89 | 62±7.39 | 81±5.99 | 92±7.19 | 67±7.19  |
| GSH       | 5.6±1.49 | 5.8±2.79 | 6.3±2.49 | 9.2±1.39 | 9.8±1.29 | 5.1±1.29 |
| CAT       | 214±13.69 | 219±15.49 | 230±13.29 | 128±14.39 | 104±159 | 201±14.79 |
| Heart     |         |    |     |     |         |          |
| SOD       | 49±29.69 | 47±25.49 | 44±28.79 | 47±22.69 | 60±16.99 | 49±18.69 |
| MDA       | 103±5.99 | 108±4.29 | 106±5.59 | 108±3.99 | 107±5.42 | 102±1.44 |
| GSH       | 12±0.079 | 12±0.079 | 12±0.059 | 12±0.069 | 13±0.069 | 12±0.059 |
| CAT       | 62.2±3.49 | 64.3±3.59 | 65.1±2.79 | 61.4±2.39 | 54±2.79 | 63±3.19 |

n=5. Values (P<0.05).
animals. Treatment with Q5 alone had no effect on any of these parameters, whereas the Q10 increased SOD activity and MDA level, and had no effect on CAT activity and GSH level in the brain. All the investigated parameters in the heart, kidney, and liver tissues were not affected by treatment with Q10 alone. Histological study as shown in Figures 2-5 demonstrates normal cerebellum [Figures 2a-d] and cerebrum [Figures 3a-d] of control and treated animals with no visible lesion. On the other hand, severe congestion with marked interstitial cellular infiltration was noted in the kidney ATZ-treated animals, whereas no visible lesions were observed in the control and the combine exposure group [Figures 4a-d]. The liver of the control [Figure 5a], Q5-treated [Figure 5b] and Q10-treated [Figure 5c] animals showed normal morphology, whereas those of the ATZ-treated rats showed mild diffuse vacuolar degeneration of hepatocytes [Figure 5d] and those of the ATZ + Q5 showed mild periportal cellular infiltration by mononuclear cells [Figure 5c]. The liver histology of the ATZ + Q10 resembles those of the control, Q5, or Q10 groups [Figure 5f].

Our previous research on effects of combined administration of ATZ (120 mg/kg) and QT (20 mg/kg) to adult rats revealed potentiation of oxidative stress in the rat liver and reproductive organs (testis and epididymis) in terms of alteration of antioxidant enzymes and lipid peroxidation level.[22,24] As a follow-up, the present studies were initiated with lower doses of QT (5 or 10 mg/kg) with the intention of selecting appropriate dose of QT that can protect against ATZ-induced oxidative stress, not only in the liver but also in the brain, kidney, and heart, and eventually put the QT effects at low and high doses into connection. Liver is the first target of ingested oxidants and also very important

Figure 1: Effects of atrazine and quercetin on serum enzyme levels of rats. (a) Alkaline phosphatase (ALP), (b) Sorbitol dehydrogenase (SDH), (c) Acid phosphatase (ACP), (d) Aspartate amino transferase (AST). (Mean ± standard deviation (SD), n = 6 except in Q5 + atrazine (ATZ) where n = 5). * vs control, ** vs all groups (P < 0.05)

Figure 2: Representative photomicrograph of hematoxylin and eosin-stained sections of cerebellum of control and experimental rats showing normal morphology in all groups. (a) Control, (b) Quercetin, 5 mg/kg, (c) Atrazine, (d) Quercetin, 5 mg/kg + atrazine (×400)

Figure 3: Representative photomicrograph of hematoxylin and eosin-stained sections of cerebrum of control and experimental rats showing normal morphology in all groups. (a) Control, (b) Quercetin, 5 mg/kg, (c) Atrazine, (d) Quercetin, 5 mg/kg + atrazine (×400)

Figure 4: Representative photomicrograph of hematoxylin and eosin-stained sections of kidney of control and experimental rats (a) Control, (b) Quercetin, 10 mg/kg, (c) Atrazine, (d) Quercetin, 10 mg/kg + atrazine. (Arrow: Severe congestion with marked interstitial cellular infiltration (×400)
tissue in defense against oxidative stress. Heart, kidney, and brain also possess antioxidant defense and alterations in the activity of antioxidant enzymes in these tissues in rats exposed to pesticides are known. Therefore, in this study we also measured the antioxidant status in the different tissues and liver indirectly, by measuring the activities of CAT and SOD; GSH and MDA levels as indicators of susceptibility to oxidative stress in rats.

Our results showed that ATZ increased MDA formation in the liver, brain, and kidney but not in the heart. The activities of SOD and CAT decreased in the liver and kidney, increased and decreased, respectively, in the brain, and remains unchanged in the heart. GSH level was not affected in all the tissues except in the liver where the level was increased. These clearly support our previous studies and those of others that ATZ was able to induce oxidative stress in these tissues. The increased activity of SOD in the brain and decreased activity in the kidney and liver with the simultaneous decrease in CAT activity and escalated MDA concentration in these tissues allow us to conclude that the brain, liver, and kidney antioxidant defense system was impaired leading to the elevated lipid peroxidation. The differential response in SOD and CAT activities in these tissues confirms the existence of an inducible antioxidant system, and is known to be an adaptive response to oxidative stress. GSH levels were not changed in all the tissues except the liver where the level was increased. The unchanged GSH levels in the kidney and brain have also been reported by us in the testis and epididymis, suggesting the differential tissue responsiveness of GSH in ATZ-induced oxidative stress in the liver. Because the antioxidative enzymes, GSH, and MDA levels were unchanged in the heart, it indicates that the heart tissue was completely resistant to ATZ-induced oxidative stress. Overall, the fluctuated levels in the antioxidant enzymes, GSH, and MDA concentrations in the various tissues of rats treated with ATZ may be dependent on the differences between interstitial concentrations. In other words, the tissues might have to be exposed to different ATZ concentration due to blood volume differences in the tissues.

Co-administration of Q5 did not prevent the increased levels in the serum-marker enzymes caused by ATZ. With respect to the oxidative stress parameters, Q5 normalized SOD and MDA in the brain but not CAT. This protective response on SOD and MDA was not seen in the kidney and liver. In the heart, SOD activity was enhanced, CAT activity was decreased but MDA level and both brain and heart tissues GSH remain unchanged when compared with the vehicle control or the ATZ-treated rats. Furthermore, the combine effects of Q5 + ATZ did not recover CAT activity in the kidney and further decreased the activity in the liver, suggestive of synergistic effect of ATZ and Q5 with respect to CAT activity. It may seem that Q5 effectively protect the brain against ATZ-induced lipid peroxidation but not the kidney and liver. The increased SOD activity in the heart with the simultaneous decrease in the activity of CAT along with the unchanged MDA concentration allow us to conclude that the heart antioxidant defense system still effectively protects from the action of the interactive effects of Q5 + ATZ-induced oxidative stress. Q5 alone had no effect on any of the measured biochemical variables, whereas Q10 alone increased SOD in the brain. The increase in the SOD activity, which is indicative of a protective response to oxidative stress is consistent with the elevated MDA concentration in the brain. We suggest that this dose of QT might have a pro-oxidant effect in the brain. The activities of antioxidant enzymes have also been reported to be inhibited or increased by QT depending on the experimental model and dose. The brain exhibits high oxygen consumption and are enriched with polyunsaturated fatty acids, so it is quite vulnerable to lipid peroxidation. There exists, thus, a possibility in our experimental model that the brain would be more vulnerable to quercetin-induced oxidative stress even at a dose that would be incapable of inducing the same effect in other tissues.

Figure 5: Representative photomicrograph of hematoxylin and eosin-stained sections of liver of control and experimental rats (a) Control, (b) Quercetin, 5 mg/kg, (c) Quercetin, 10mg/kg, (d) Atrazine, (e) Quercetin, 5 mg/kg + atrazine (f) Quercetin, 10 mg/kg + atrazine. (Arrows: [d] Mild diffuse vacuolar degeneration of hepatocytes, [e] mild perportal cellular infiltration by mononuclear cells). (×400)
Q10 is thought to act as effective cytoprotectant in the kidney and liver since it prevented the cellular injury, oxidative stress, and subsequently inhibited the leakage of these enzymes (SDH, ACP, ALP, and AST) into the blood circulation. The induced hepatic GSH levels; decreased CAT activities in the brain, kidney, and liver; decreased SOD activity in the kidney, liver, and heart but not the brain of the Q10 + ATZ-treated animals were comparable to the control values. The inability of Q10 to effectively restore brain SOD activity as was observed in the Q5 + ATZ-treated animals was consistent with the elevated level of MDA. It is probable that QT exhibits better antioxidant effect in the brain when its concentration is low, while in other tissues like the liver and kidney, a higher dose of QT would be required for QT to be an effective antioxidant. However, this dose would still be within a narrow therapeutic concentration range, because at doses of QT equal to 20 mg/kg body weight, QT becomes a pro-oxidant in the liver and reproductive organs when co-administered with ATZ. Thus, ATZ and QT are good models to study in vivo combined effects, and especially synergistic effects for pesticides and flavonoids.

As most of the histological changes observed in the present study were noted in the kidney and less in the liver and also with the cerebrum and cerebellum maintaining a normal morphology similar to the control, the elevated serum-marker enzymes could be most likely due to the renal damage. It is also possible that the slight degeneration of hepatocytes in the ATZ-treated rats and/or mild perportal cellular infiltration by mononuclear cells in the ATZ + Q5-treated rats were sufficient to induce the release of the serum markers from the liver into the systemic circulation which was completely prevented on co-administration of Q10. The susceptibility of renal tissues to the toxic effects of noxious chemicals can be attributed in part to the differences in the anatomic and physiologic features of this organ. For instance, under resting state, the tissue to damage caused by the noxious chemical under the renal damage, it may in fact predispose or not protect another tissue to damage caused by the noxious chemical under the same experimental condition.

In conclusion, lipid peroxidation in terms of MDA levels are more intensified in renal tissues of Q5 + ATZ than those of Q10 + ATZ animals and are prevented in the hepatic tissues of Q10 + ATZ, and exacerbated in those of the Q5 + ATZ-treated rats. Furthermore, the fluctuation in the constituent antioxidative system in the tissues of the Q10 + ATZ-treated animals was markedly less advanced than in those observed in the Q5 + ATZ animals, but the brain tissues of these animals were vulnerable to lipid peroxidation. Hence Q10 is more beneficial in reversing ATZ-induced hepatic and renal damage. With regards to particular tissue, Q5 is a better effective dose for protecting against ATZ-induced lipid peroxidation in the brain, whereas Q10 is a better effective dose for preventing ATZ-induced changes in the kidney and liver antioxidant defense system while the heart seems less susceptible to ATZ- and Q5 + ATZ-induced oxidative stress. Thus, the differential protective effect of QT on the antioxidant defense system could be that the antioxidant system might have to be exposed to different concentrations of QT due to blood volume/physiologic/anatomic differences in the tissues. Regarding the symptoms shown by these animals (Q5 + ATZ) including lethargy and decreased body weight, and finally death allow us to suppose that the health conditions of these animals (Q5 + ATZ) are not normal and indicative of presence of general toxicity. Therefore, when a bioactive compound such as quercetin protects a target tissue from a chemically induced oxidative damage, it may in fact predispose or not protect another tissue to damage caused by the noxious chemical under the same experimental condition.

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