



Biochemical Evaluation of the Effects of Quercetin On Experimental Acute Methanol Intoxication in Rats

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Authors' contributions

This work was carried out in collaboration among all authors. Author HHK designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors İK and AÖ managed the analyses of the study. Authors HHK, İK and AÖ managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Previous studies have shown the role of oxidative stress in methanol toxicity. Also, studies have shown antioxidant, anti-inflammatory effects of quercetin (Q). This study evaluates the effect of quercetin (Q) administration on total oxidant status (TOS), total anti-oxidant status (TAS), oxidative stress index (OSI) and paraoxanase 1 (PON1) levels in rats with experimentally-induced methanol (MeOH) intoxication. Six groups were constituted as control, methotrexate (Mtx), Mtx+MeOH, Mtx+MeOH+ethanol (EtOH), Mtx+MeOH+Q1, Mtx+MeOH+Q2. All rats except controls were injected Mtx (0.3 mg/kg daily) intra-peritoneally (IP) for 7 days. On the 8th day of the test, 3 g/kg MeOH was injected IP in MeOH, EtOH and Q groups. Four hours after MeOH administration, 0.5 g/kg EtOH was injected IP in EtOH group and 50 mg/kg Q was administered IP in Q1 and Q2 groups. In addition, a total of 5 doses of 50 mg/kg Q was injected IP 24, 48, 72 and 96 hours after the first dose in Q2 group. Saline solution was given IP in the other groups. Rats were sacrificed

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with anesthesia 8 hours after the administrations. Blood samples were obtained for evaluating total oxidant status (TOS), total anti-oxidant status (TAS), oxidative stress index (OSI) and paraoxanase 1 (PON1) levels. The highest TOS level was found in MeOH+MTx group. A significant reduction was detected in serum TOS levels in MeOH+Mtx+EtOH, MeOH+Mtx+Q1 and MeOH+Mtx+Q2 groups. The lowest serum TAS level was detected in MeOH+Mtx group. Maximum TAS level elevation was found in MeOH+Mtx+Q2, MeOH+Mtx+Q1 and MeOH+Mtx+EtOH groups. The highest OSI ratio was found in MeOH+Mtx group. A reduction was detected in OSI ratios in MeOH+Mtx+EtOH, MeOH+Mtx+Q1 and MeOH+Mtx+Q2 groups as compared to MeOH+Mtx group. The lowest serum PON1 level was found in MeOH+Mtx group. Maximum serum PON1 level elevation was found in MeOH+Mtx+Q2 group. The results indicating that quercetin administration could be effective on both acute and subacute processes of methanol intoxication were tried to be revealed through serum TOS, TAS, OSI and PON1 levels. These results show that quercetin could be used as an alternative treatment option in methanol intoxication.

Keywords: Methanol; quercetin; TOS; TAS; OSI; PON1.

1. INTRODUCTION

Methanol (MeOH) intoxication is an important public health problem because its toxicity may cause severe morbidity and mortality. MeOH toxicity has been widely studied since it has been recognized as a serious neurotoxin in humans. MeOH is rapidly absorbed from the gastrointestinal and respiratory tracts, as well as through the skin. MeOH is metabolized to formaldehyde which is subsequently converted into formic acid in the liver. Formic acid is responsible for the toxic effects of MeOH intoxication. Formic acid inhibits cellular respiration and contributes to metabolic acidosis. Moreover, MeOH induces lipid peroxidation and depletes the free radical scavenging enzyme systems. Treatment is based on the inhibition of alcohol dehydrogenase enzyme that is the first step of formic acid conversion as formic acid is the substance responsible for methanol intoxication. Ethanol and fomepizole of which affinity to alcohol dehydrogenase enzyme is higher than that of methanol are used for this purpose today [1-4]. Some other treatment options, such as alpha-lipoic acid, rutin as an anti-oxidant were also reported to have promising effects in methanol-induced toxicity [5,6].

Quercetin (3,3',4',5,7-pentahydroxyflavone) is a typical representative flavonoid. The great effects of quercetin are attributed to its anti-oxidant and anti-inflammatory capacity [7,8]. Also, previous studies have shown anti-carcinogenic, anti-viral, anti-coagulation, as well as the ability to inhibit lipid peroxidation, oxygen radical-scavenging activity and to stimulate mitochondrial biogenesis immunomodulatory [9]. Polyphenolic nature of quercetin has been reported to exhibit various

neuroprotective properties due to its antioxidant activity and also has the ability to scavenge free radicals and reduce the risk of neurodegeneration [10]. Quercetin is found naturally in many plant-based foods, particularly in the outer layer or peel. Q is found in vegetables and fruits like capers, peppers (yellow and green), onions (red and white), shallots, cherries, tomatoes, red apples, red grapes, broccoli, berries, tea (green and black) [11].

Oxidative stress is involved in many diseases especially neurological disease. The definition of oxidative stress implies increased oxidant production and/or a decreased antioxidant capacity in animal cells characterized by the release of free radicals, resulting in cellular degeneration. The imbalance between the rate of free radical production and the antioxidant defense causes cellular damage resulting in lipid peroxidation [12]. Reactive oxygen species (ROS) are thought to play a role in a variety of physiological and pathophysiological processes in which increased oxidative stress may play an important role in disease mechanisms [13]. ROS are difficult to measure directly because of their short half-lives; therefore, it is preferable to search for and determine the indirect markers of oxidative stress. The total antioxidant status (TAS), total oxidant status (TOS), and oxidative stress index (OSI) are the key factors reflecting the redox balance between oxidation and antioxidation. TAS is an indicator of the activity of all antioxidants; TOS is an indicator of ROS; and OSI is the ratio of TOS to TAS and indicates the level of oxidative stress [14,15]. Paraoxonases are a family of three enzymes called PON1, PON2 and PON3. PON1 is the most studied enzyme of the family. PON1 has been widely studied in human medicine; initially the interest

on this enzyme arose from the toxicological point of view, by its protective role from poisoning by organophosphate derivatives. They have multifunctional roles in various biochemical pathways such as protection against oxidative damage and lipid peroxidation, contribution to innate immunity, detoxification of reactive molecules, bioactivation of drugs, modulation of endoplasmic reticulum stress and regulation of cell proliferation/apoptosis [16,17].

A growing number of experimental evidences have emerged, which support the concept that quercetin with that strong anti-oxidant and anti-inflammatory activities ameliorate oxidative stress and thereby may prevent damage to the tissues. Current data reveal that influences following acute methanol intoxication develop very rapidly and in a short duration. All this information suggests that Q will provide for the treatment of acute methanol intoxication. No studies investigating the protective effect of quercetin against acute methanol intoxication were found in the literature. Also, to the best of our knowledge, this is the first study in literature to evaluate the effect of quercetin (Q) administration on serum TOS, TAS, OSI and PON levels in rats with experimentally-induced methanol (MeOH) intoxication.

2. MATERIALS AND METHODS

This study was approved by the Necmettin Erbakan University KONÜDAM Experimental Medicine Application and Research Center.

2.1 Animals

A total of 52 albino Wistar Albino male rats weighing 280-320 g were used in the experiments. Animals were kept and fed at normal room temperature (22°C) prior to the experiment.

2.2 Chemicals

Methotrexate (MTX, Koçak Farma, İstanbul, Turkey) was diluted in saline. MeOH, ethanol and thymoquinone were purchased from Sigma Chemical Co (St. Louis, MO). MeOH and ethanol were diluted in saline, and administered as a 20% w/v solution. Quercetin was dissolved in 0.9 % saline.

2.3 Experimental Groups

This study included six groups, each containing nine rats except control group

were seven rats. The groups were control, Mtx, Mtx+MeOH, Mtx+MeOH+ethanol, Mtx+MeOH+Q1, Mtx+MeOH+Q2.

2.4 Experimental Procedure

Liver folate content is higher and folate metabolism is faster in rats as compared to humans. So it is difficult to develop formic acid accumulation and metabolic acidosis. Methotrexate (Mtx) was shown to reduce folate content in rats in experimental studies [5]. Therefore all rats except controls were administered Mtx 0.3 mg/kg daily for 7 days for developing methanol intoxication in rats similar to humans and for slowing formate metabolism. At the 8th day of the experiment, i.p. injection of MeOH (3 g/kg) was administered in MeOH, EtOH, Q groups. Four hours after MeOH treatment, 0.5 g/kg EtOH was injected i.p. in EtOH group; 50 mg/kg Q i.p. in Q1 and Q2 groups. In addition, a total of 5 doses of 50 mg/kg Q was injected IP 24, 48, 72 and 96 hours after the first dose in Q2 group. Saline solution was given IP in the other groups. Rats were sacrificed with 50 mg/kg ketamin HCl anesthesia 8 hours after the administrations. Blood samples were obtained for evaluating total oxidant status (TOS), total anti-oxidant status (TAS), oxidative stress index (OSI) and paraoxanase 1 (PON1) levels.

2.5 Biochemical Analysis

Venous blood samples were collected by centrifugation at 4 °C and 1000 g for 10 minutes to separate serum. Serum samples were stored at -80 °C until the parameters were studied.

2.6 Measurement of Total Antioxidant Status

Serum TAS levels were measured by colorimetric method using a commercially available kit (Rel Assay Diagnostics, Gaziantep, Turkey). The results were expressed in mmol H₂O₂ Eq./L.

2.7 Measurement of Total Oxidant Status

Serum TOS levels were measured by colorimetric method using a commercially available kit (Rel Assay Diagnostics, Gaziantep, Turkey). The results were expressed in μmol H₂O₂ Eq./L.

2.8 Oxidative Stress Index (OSI)

The OSI value was calculated according to the following formula: OSI = TOS/TAS; the OSI, an indicator of the degree of oxidative stress.

2.9 Measurement of Paraoxonase-1 Activity

Serum PON-1 levels were measured by colorimetric method using a commercially available kit (Rel Assay Diagnostics, Gaziantep, Turkey). The results were expressed in U/L.

2.10 Statistical Analysis

Kolmogorov Smirnov test was used for the parametric distribution of numerical parameters. All data are expressed as mean \pm standard error of the mean ($x \pm$ SEM). Biochemical results were analyzed using SPSS version 20 software (SPSS, Chicago, IL). Difference of variances between the groups was analyzed by ANOVA followed by post-hoc Tukey test.

3. RESULTS

At the end of the study, all rats were evaluated without any failure. Serum TOS, TAS, OSI and PON1 levels of the groups are presented in Table 1.

The highest TOS level was detected in MeOH+Mtx group and this elevation was statistically significant as compared to control and Mtx groups ($p < 0.001$). A reduction was detected in TOS levels in treatment groups (MeOH+Mtx+EtOH, MeOH+Mtx+Q1, MeOH+Mtx+Q2) as compared to intoxication group (MeOH+Mtx) and the difference was statistically significant ($p < 0.001$, $p < 0.001$ and $p < 0.001$, respectively). The reduction in TOS levels in MeOH+Mtx+Q2 group as compared to MeOH+Mtx+Q1 group was statistically significant ($p < 0.001$).

The lowest serum TAS level was found in MeOH+Mtx group and the difference was statistically significant as compared to control and Mtx groups ($p < 0.001$ and $p: 0.086$, respectively). Maximum TAS level elevation was found in MeOH+Mtx+Q2 group and the elevation was statistically significant as compared to MeOH+Mtx+EtOH group ($p < 0.001$). A statistically significant difference was not detected between MeOH+Mtx+Q2 group and MeOH+Mtx+Q1 group with regard to TAS level elevation ($p: 0.266$).

The highest OSI ratio was detected in MeOH+Mtx group and the difference was statistically significant as compared to control and Mtx groups ($p < 0.001$). A reduction was detected in OSI ratios in treatment groups (MeOH+Mtx+EtOH, MeOH+Mtx+Q1,

MeOH+Mtx+Q2) as compared to intoxication group (MeOH+Mtx) and the difference was statistically significant ($p < 0.001$, $p < 0.001$ and $p < 0.001$, respectively). The lowest OSI levels were found in MeOH+Mtx+Q2, MeOH+Mtx+Q1 groups, respectively; however the difference was not statistically significant ($p: 0.1$).

The lowest serum PON1 level was found in MeOH+Mtx group and the difference was statistically significant as compared to control and Mtx groups ($p < 0.001$). Maximum serum PON1 level elevation was found in MeOH+Mtx+Q2 group. The elevation was significant as compared to the intoxication group (MeOH+Mtx) and treatment groups of MeOH+Mtx+EtOH and MeOH+Mtx+Q1 ($p < 0.001$, $p: 0.040$ and $p: 0.010$, respectively).

4. DISCUSSION

It was aimed to evaluate the effects of quercetin administration on serum TOS, TAS, OSI and PON1 levels in rats with experimentally-induced acute MeOH intoxication.

Formic acid leads to a reduction in ATP synthesis, an elevation in reactive oxygen species (ROS) and cell death directly or through inhibiting cytochrome oxidase found in mitochondrial respiratory chain. Reactive oxygen species are continuously produced during normal physiologic events and removed by antioxidant defense mechanism. The imbalance between reactive oxygen species and antioxidant defense mechanisms leads to lipid peroxidation and oxidative damage [1,3].

TOS, TAS, and OSI are the key factors reflecting the redox balance between oxidation and anti-oxidation. TOS is an indicator of ROS; TAS is an indicator of the activity of all antioxidants; and OSI is the ratio of TOS to TAS and indicates the level of oxidative stress [11,12]. TOS reflects the overall effect of the oxidants in body fluids and plasma. The highest TOS level was found in MeOH+Mtx group. Detecting a significant reduction in TOS levels in treatment groups (MeOH+Mtx+EtOH, MeOH+Mtx+Q1, MeOH+Mtx+Q2) as compared to intoxication group (MeOH+Mtx) show that methanol toxicity leads to oxidative stress in rats, and quercetin and ethanol administration reduces methanol toxicity-related oxidative stress. Besides, more evident TOS level reduction in MeOH+Mtx+Q2 as compared to MeOH+Mtx+Q1 and MeOH+Mtx groups has revealed that repeated doses of quercetin administration reduces oxidative stress more effectively.

Table 1. Comparison of the TOS, TAS, OSI and PON1 levels in serum

Groups	TOS (mmol Trolox Eq./L.)	TAS (μ mol H ₂ O ₂ Eq./L.)	OSI (OSI = TOS/TAS)	PON1 (U/L.)
I-Control	6,61 \pm 0,19	0.85 \pm 0,41	7,72 \pm 0,48	66,88 \pm 1,79
II-MTX	8,04 \pm 0,42	0.65 \pm 0,58	12,39 \pm 1,84	48,47 \pm 4
III-MeOH+MTX	14,16 \pm 1,28	0.58 \pm 0,98	24,99 \pm 5,87	35,32 \pm 2,83
IV-MeOH+MTX+EtOH	10,72 \pm 0,93	0.80 \pm 0,079	13,64 \pm 2,52	42,95 \pm 1,88
V-MeOH+MTX+Q1	8,72 \pm 0,15	0.90 \pm 0,06	9,70 \pm 0,77	40,96 \pm 1,40
VI-MeOH+MTX+Q2	8,03 \pm 0,38	0.95 \pm 0,11	8,61 \pm 1,65	48,66 \pm 6,93
<i>P</i> values				
I-II	<0.001	<0.001	<0.001	<0.001
I-III	<0.001	<0.001	<0.001	<0.001
I-IV	<0.001	0.093	<0.001	<0.001
I-V	<0.001	0.097	<0.001	<0.001
I-VI	<0.001	0.039	0.159	<0.001
II-III	<0.001	0.086	<0.001	<0.001
III-IV	<0.001	<0.001	<0.001	<0.001
III-V	<0.001	<0.001	<0.001	<0.001
III-VI	<0.001	<0.001	<0.001	<0.001
IV-V	<0.001	0.008	0.001	0.023
IV-VI	<0.001	0.005	<0.001	0.040
V-VI	<0.001	0.266	0.1	0.010

Total anti-oxidant capacity (TAS) is a stronger antioxidant parameter as it reflects total anti-oxidant capacity instead of the individually measured anti-oxidant substances or enzymes. While the lowest serum TAS level was detected in MeOH+Mtx group, maximum TAS level elevation was detected in MeOH+Mtx+Q2 group. TAS level elevation in MeOH+Mtx+Q2 and MeOH+Mtx+Q1 groups was more evident as compared to MeOH+Mtx+EtOH group. The results of the study have revealed that quercetin and ethanol administration increased anti-oxidant capacity against oxidative stress caused by methanol toxicity. This improvement was more evident in MeOH+Mtx+Q2 group in which repeated doses were applied.

OSI, indicates the level of oxidative stress. The highest OSI ratio was detected in MeOH+Mtx group. The significant reduction in OSI ratios in treatment groups (MeOH+Mtx+EtOH, MeOH+Mtx+Q1, MeOH+Mtx+Q2) as compared to intoxication group (MeOH+Mtx) has revealed that both quercetin and ethanol administration reduced oxidative stress. Besides, repeated doses of quercetin reduced oxidative stress more effectively.

PON1 is an enzyme that has a role in anti-oxidant system against cellular damage through hydrolyzing lipid peroxides. The lowest serum PON1 level was found in MeOH+Mtx group. Maximum serum PON1 level elevation was found in MeOH+Mtx+Q2 group. The results

reveal the anti-oxidant role of quercetin administration against lipid peroxidation and this effect becomes more evident in repeated doses.

No studies investigating the protective effect of quercetin against acute methanol intoxication were found in the literature. In addition, repeated doses of quercetin administration are not seen to be studied in efficiency measurement studies until today. We want to state that the results of the present study are valuable for studies about the treatment of methanol intoxication that leads to severe and irreversible damages particularly in neuronal tissues [18,19].

Studies have shown antioxidant, anti-inflammatory, and especially neuroprotective effects of quercetin in different models of neurodegeneration and neurotoxicity. It is thought that quercetin's recovery effect on the neural tissue occurs via promotion of neurogenesis and nerve-regeneration, in addition to prevention of neuronal degeneration due to its antioxidant and anti-inflammatory activities [20-23].

5. CONCLUSION

It was aimed to reveal that quercetin treatment could be effective both in acute and sub-acute processes of methanol intoxication through serum TOS, TAS, OSI and PON1 levels in the

present study. These results may show that quercetin could be used as an alternative treatment in methanol intoxication. Also, further studies that examine serum, tissue and histopathological data together are required in order to clearly reveal the effects of quercetin treatments on MeOH metabolism.

CONSENT

It is not applicable.

ETHICAL APPROVAL

Animal Ethic committee approval has been collected and preserved by the author(s)

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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