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Effects of coenzyme Q10 and N-acetylcysteine on the expression of apoptotic biomarkers and histopathological findings in the permethrin-induced hepatotoxicity in rats

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ABSTRACT

Permethrin (PMT) is a synthetic pyrethroid insecticide widely applied in the agriculture and animal husbandry industry. The current study focused on the evaluation of the oxidative damage and apoptosis induced by PMT, as well as the protective role of coenzyme Q10 and N-acetylcysteine (NAC) against PMT toxicity in the liver of male rats. In this study, rats were divided in four groups, including G_1 (control), G_2 (PMT), G_3 (NAC + PMT), and G_4 (Q10 + PMT). Levels of malondialdehyde (MDA) and total antioxidant capacity (TAC) were measured. RT-PCR was adopted to study the expression of *Bax*, *Bcl2, p53, Caspases-3* and *-9* genes. PMT exposure significantly decreased FRAP value, whereas increased MDA content in the liver tissue ($p < 0.001$). While *Bcl2* was downregulated (5.31-fold), permethrin increased the expression of *Bax* (4.84-fold), *p53* (4.67-fold), *Caspases-3* (6.21-fold) and *Caspases -9* (6.36-fold) genes in exposed group ($p<0.001$). Both Q10 and NAC significantly improved FRAP values and decreased MDA level. Unlike the apoptotic genes, *Bcl2* expression was significantly reversed after NAC and Q10 therapy ($p < 0.001$). In conclusion, PMT exposure induced oxidative stress and liver cells' apoptosis. Q10 and NAC can mitigate toxic effects of PMT and consequently protect liver damage.

Keywords: Permethrin, Q10, NAC, Oxidative stress, Apoptosis.
Article type: Research Article.

INTRODUCTION

Permethrin (PMT) is one of the most widely used type 1 synthetic pyrethroids worldwide. This insecticide targets voltage-dependent sodium channels (VDSCs), delays their inactivation and leads to neurotoxicity effects and eventually death. Studies show that PMT can cause various toxic effects such as teratogenicity, cardiotoxicity, endocrine dysfunction, hepatotoxicity and cytotoxicity in both vertebrates and non-vertebrates (Dymond & Swift 2008). However, the exact mechanism of PMT mediated toxicological effects remains unclear. Oxidative stress is widely reported as a possible mechanism of PMT toxicity (Palipoch 2013). Oxidative stress which is the result of an imbalance between the antioxidants and free radicals induces serious intracellular damages such as DNA breaks, protein and lipid oxidation, cell membrane integrity and consequently cell apoptosis (Colagar *et al.* 2009; Al-badry 2022; Parpieva *et al.* 2023). Due to the fact that antioxidants have the capacity to control the pathologic effects of intracellular ROS, their consumption can be considered as an effective approach in managing a variety of disorders (Beigi Harchegani *et al.* 2020). Since PMT probably conducts its toxicity by promoting free radical formation, it seems that antioxidant therapy would be a productive method in cell protection. N-acetylcysteine is

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the acetylated form of amino acid cysteine and thanks to its thiol groups, it is highly considered for replenishing the glutathione (GSH) reservoirs (Sadat 2014). Historically, NAC has been broadly administrated for treatment of a variety of diseases such as human immunodeficiency virus (HIV), chronic obstructive pulmonary disease (COPD), nephropathy, brain disorders, Alzheimer's disease and even mental illness (Shimizu *et al.* 2017). Having a free radical scavenging property, NAC is noticeably efficient in treatment or prevention of numerous disorders including cancer and diabetes (Wang *et al.* 2011). Coenzyme Q10 is another compound that is present naturally in the body. It is a lipophilic compound and plays a remarkable role in transferring electrolytes through mitochondria (Crane 2001). Q10 is not only essential for intracellular ATP production, but also plays a high antioxidant and anti-inflammatory role within cells (Schmelzer *et al.* 2008). Prescription of Q10 has been documented in a variety of disorders, including Q10 deficiency, mitochondrial disorders, cardiovascular and neurology diseases (Garrido-Maraver *et al.* 2014). Therefore, due to the high antioxidant capability of NAC and Q10, this study aimed to investigate protective effects of these supplements in the liver tissue of rats exposed to PMT. Correspondingly, the effects of NAC and Q10 on histopathological alterations, as well as the expression of apoptotic genes, including *Bax, Bcl2* and *caspases-3* and *-9* as well as protein *P53* were also investigated.

MATERIALS AND METHODS

Animals

Twenty-four male Wistar rats (2-3 months of age, 150-200 g) were purchased (Pasteur Institute, Iran) and housed in standard condition (temperature 22 ± 2 °C, humidity 50% ± 5%, and a 12:12 light/dark cycle) with a free access to food and water. Rats were then randomly divided into 4 groups including control (G_1), PMT (G_2), PMT + NAC (G_3) and PMT + Q10 (G_4).

Treatments

NAC and Q10 (Merck, Germany) were freshly prepared daily before experiment. In G_2 group, animals were fed with a continuous dose of PMT solution (12.5 mg kg^{-1}), while rats in G_3 and G_4 groups, treated with an additional dose of NAC (50 mg kg^{-1}) and Q10 (50 mg kg^{-1}) respectively. Untreated animals in G_1 were only fed with normal pellets and water. This study lasted four weeks and the treatments were performed in every other day and in accordance with the ethical issues.

Samples collection

Animals were anesthetized with a combination of xylazine (10 mg kg^{-1}) and ketamine (30-50 mg kg^{-1}) 2 days after the last treatment. Tissue samples were collected for histopathological examinations (in tubes containing 10% formalin) and gene expression analysis (RNA later was added to micro tubes). Turning to the former one, after storing for a week in 10% formalin, samples were dehydrated using a graded series of ethanol and then embedded in paraffin. Tissue sections were then prepared using a manual microtome (HistoCore Biocut, USA) at 5µm of thickness and stained with haematoxylin-eosin (H & E). Histopathological alterations were recorded by light microscopy (Eclipse E200, USA). For evaluation of the gene expressions, about 150 mg of liver tissues were removed. Samples were then homogenized and centrifuged at 12000 rpm/4 °C for 15 min (Ma *et al.* 2017; Larki *et al.* 2020). The removed supernatants were then stored at -80 °C for further experiments.

Biomarkers of oxidative

Total antioxidant capacity (TAC) was measured by FRAP 9-ferric method (for reducing antioxidant power) which was previously described by Benize *et al.* 1996). Thiobarbituric acid (TBA) method was used for measurement of malondialdehyde (MDA; Rao *et al.* 1989).

Gene expression analysis

The RNX-Plus Kit (SinaClon; RN7713C) was used for total RNA extraction and complementary DNA was synthesized using Revert Aid Reverse Transcriptase (Thermo Science, Germany) and random hexamer primers (Thermo Science, Germany) at 42 ℃ for 1 h. Amplifications was then performed using a Rotor Gene 6000 (Corbett, Australia) thermocycler. An aliquot of 5 µm of master mix along with 100 nM primers were applied for each reaction in 40 cycles of amplification. GAPDH was considered as the reference gene and relative expressions of genes was calculated using 2-ΔCt method. Primer sequences of studied genes are shown in Table 1.

Table1. Primer sequences of studied genes.

Gene name	Forward sequence	Reverse sequence
Bax	5'-GAGGATGATTGCTGATGTGGATA-3'	5'-CAGTTGAAGTTGCCGTCTG-3'
Bcl2	5'-GAGGATTGTGGCCTTCTTTG-3'	5'-AGGTACTCAGTCATCCACA-3'
Caspase-3	5'-AAGCCGAAACTCTTCATCATTCA-3'	5'-GCCATATCATCGTCAGTTCCAC-3'
Caspase-9	5'-ACAAGGCCTTCGACAGTG-3'	5'-GTACCAGGAACCGCTCTT-3'
P53	5'-GTATTTCACCCTCAAGATCC-3'	5'-TGGGCATCCTTTAACTCTA-3'
GAPDH	5'-AAGTTCAACGGCACAGTCAAGG-3'	5'-CATACTCAGCACCAGCATCACC-3'

Statistical analysis

One-Way ANOVA: Post Hoc-Tukey test was selected to compare data (SPSS version 22) between the study groups and p-value < 0.05 was considered as significant.

RESULTS AND DISCUSSION

Fig. 1. illustrates histological findings of liver tissue in different groups. According to our observations, in comparison with healthy animals, PMT (G_2 group) induced an inflammatory response in the liver parenchyma and portal space where the aggregation of inflammatory cells was documented. The NAC (G_3) and Q10 (G_4) therapies mitigated these abnormalities indicating their anti-inflammatory effects. Combined therapy with NAC or Q10 remarkably decreased the rate of inflammation in rats exposed to PMT (Fig. 1). A comparison of FRAP mean values in the liver tissue of all groups is shown in Fig. 2. Rats treated with PMT exhibited significantly lower FRAP mean values (184.95 ± 62.36 µg mL^{-1}) compared to the other groups ($p < 0.001$), while its mean level in control group (438.18 ± 73.29 µg mL^{-1}) was remarkably higher than that in other groups ($p < 0.001$). The NAC and Q10 supplementations significantly improved FRAP values in rats exposed to PMT (376.41 ± 53.69 µg mL^{-1} and 381.15 ± 69.73 µg mL^{-1}, respectively; $p < 0.001$). As shown in Fig. 3, mean levels of MDA in healthy animals (9.37 ± 2.14 µg mL^{-1}) were noticeably lower compared to the other groups ($p < 0.001$). According to our findings, long term exposure to PMT exhibited higher MDA mean values (27.12 ± 3.51 µg mL^{-1}) compared to the others ($p < 0.001$). The NAC and Q10 supplementations (in G_3 and G_4) markedly declined levels of MDA in PMT-exposed rats (14.76 ± 2.69 µg mL^{-1} and 13.15 ± 2.73 µg mL^{-1}, respectively; $p < 0.001$; Fig. 3). The expression patterns of *Bax, Bcl2, Caspase 3, Caspase 9* and *P53* genes were sharply different between groups. In G_2 group, *Bcl2* expression was dramatically dropped ($p < 0.001$), while an overexpression of *Bax, Caspase 3, Caspase 9* and *P53* genes was observed in comparison with other groups ($p < 0.001$). However, in both G_3 and G_4, the expression of aforementioned genes were significantly improved. Compared to control group, PMT significantly increased Bax expression by 4.84-fold ($p < 0.001$). In contrast, rats treated with Q10 + PMT or NAC + PMT showed a significant decrease in *Bax* expression by 3.65- and 3.11-folds, respectively rather than to animals treated with PMT ($p < 0.001$; Table 2). *Bcl2* expression was markedly reduced by PMT exposure (in G_2; $p < 0.001$) compared to control group (Table 3). NAC and Q10 treatments significantly enhanced *Bcl2* expression in the liver of PMT- treated rats by 3.21- and 3.87-folds, respectively ($p < 0.001$). In comparison with G_1 group, expression of *Caspase-3* and *-9* was dramatically higher in G_2 group ($p < 0.001$). Long term administration of NAC and Q10 meaningfully decreased the expression of *Caspase 3* by 2.83- and 2.88-folds respectively (Table 4; $p < 0.001$). Moreover, after treatment with NAC and Q10, a significant reduction was found in the expression of *Caspase 9* by 3.15- and 3.70- folds respectively (Table 5; $p < 0.001$). While PMT exposure significantly increased the expression of *P53* by 4.67-fold ($p < 0.001$) compared to control, supplementation of NAC and Q10 reduced *P53* expression by 2.52- and 2.19-folds, respectively (Table 6; $p < 0.001$).

Table 2. Comparison of fold change ratio of the *Bax* expression between each group.

	Fold-change ratio	Up-/down-regulation	p-value
PMT vs. control	4.84	Up-regulated	<0.001
NAC + PMT vs. control	1.55	Up-regulated	0.081
Q10 + PMT vs. control	1.32	Up-regulated	0.51
PMT vs. NAC + PMT	3.11	Up-regulated	<0.001
PMT vs. Q10 + PMT	3.65	Up-regulated	<0.001
NAC + PMT vs. Q10 + PMT	1.17	Up-regulated	0.79

Note: $^{*}p < 0.05$ is considered as significant; One-Way ANOVA: Post Hoc-Tukey test was applied to compare mean value of *Bax* expression pattern between all groups; PMT: Permethrin; NAC: N-Acetylcysteine.

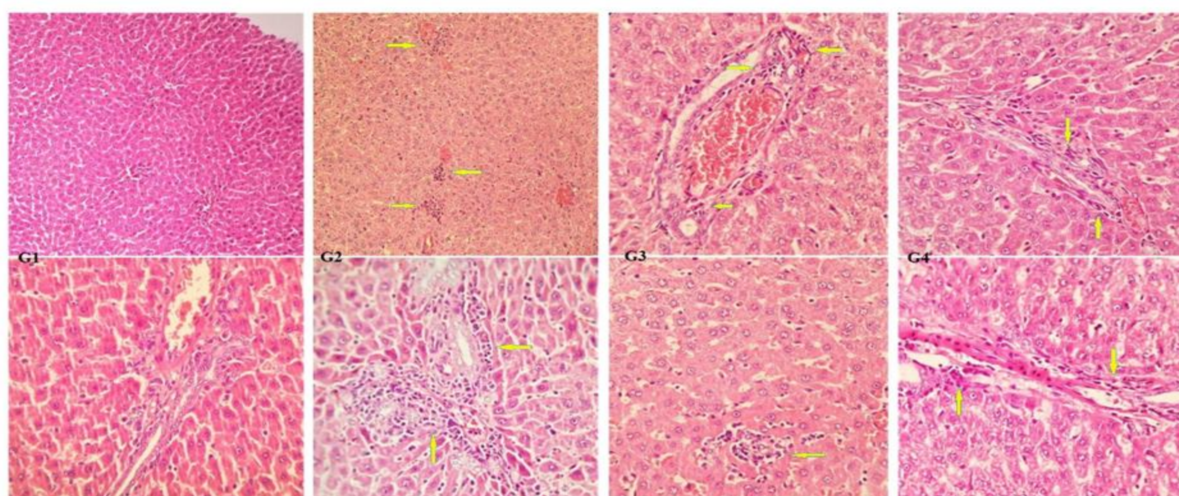

Fig. 1. Sections of liver tissue from different groups. The liver of rats in control (G_1) was normal in structure, while in PMT group (G_2) showed increased blood in the central vein, and elevated inflammatory cells. Combined therapy with NAC or Q10 declined the number of inflammatory cells along with mild inflammation in G_3 and G_4.

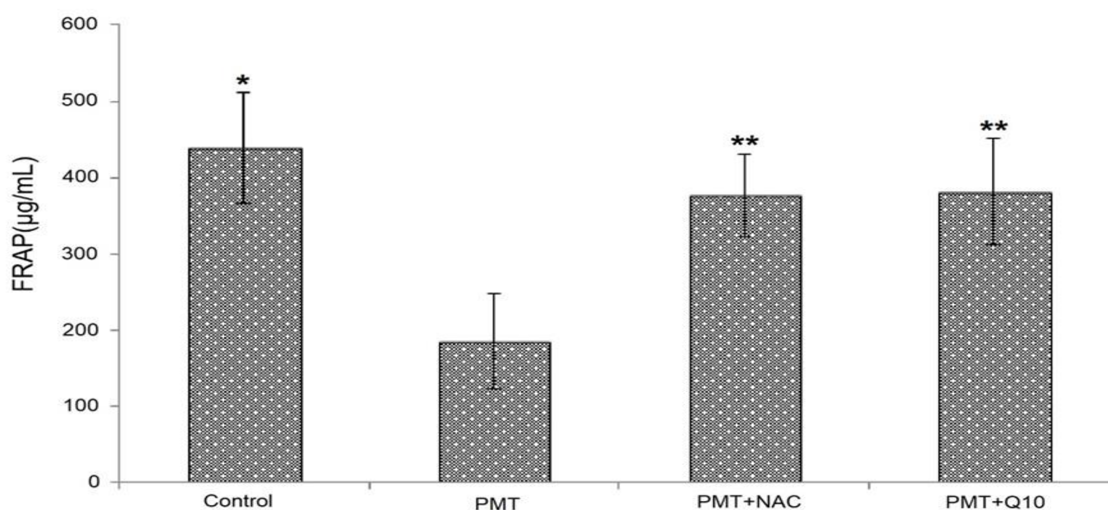

Fig. 2. Comparison of the mean of FRAP value in the liver of rats in different groups. One-Way ANOVA: Post Hoc-Tukey test was applied to compare mean value of FRAP between all groups. *p < 0.001 and **p < 0.01 compared to PMT group; PMT: Permethrin; NAC: N-Acetylcysteine.

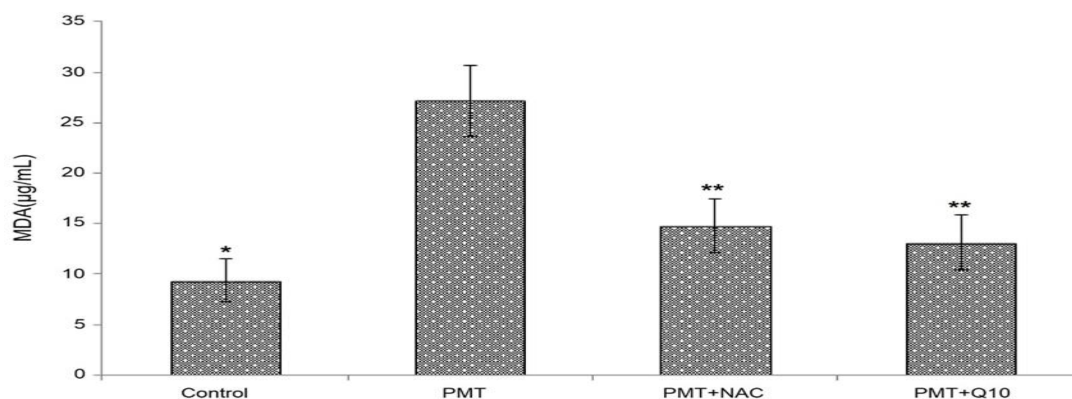

Fig. 3. Comparison of the mean of MDA levels in the liver of rats in different groups. One-Way ANOVA: Post Hoc-Tukey test was applied to compare mean value of MDA between all groups. *p < 0.001 and **p < 0.01 compared to PMT group; PMT: Permethrin; NAC: N-Acetylcysteine.

Table 3. Fold change ratio of the *Bcl2* expression in each group.

	Fold-change ratio	Up-/down-regulation	p-value
PMT vs control	5.31	Down-regulated	<0.001
NAC + PMT vs. control	1.63	Down-regulated	<0.001
Q10 + PMT vs. control	1.37	Down-regulated	0.028
PMT vs. NAC + PMT	3.26	Down-regulated	<0.001
PMT vs. Q10 + PMT	3.87	Down-regulated	<0.001
NAC + PMT vs Q10 + PMT	1.19	Down-regulated	0.059

Note: $^{*}p < 0.05$ is considered as significant; One-Way ANOVA: Post Hoc-Tukey test was applied to compare mean value of *Bcl2* expression pattern between all groups; PMT: Permethrin; NAC: N-Acetylcysteine.

Table 4. Fold change ratio of the *Caspase 3* expression in each group.

	Fold-change ratio	Up-/down-regulation	p-value
PMT vs. control	6.21	Up-regulated	<0.001
NAC + PMT vs. control	2.19	Up-regulated	0.005
Q10 + PMT vs. control	2.16	Up-regulated	0.007
PMT vs. NAC + PMT	2.83	Up-regulated	<0.001
PMT vs. Q10 + PMT	2.88	Up-regulated	<0.001
NAC + PMT vs. Q10 + PMT	1.02	Up-regulated	0.98

Note: $^{*}p < 0.05$ is considered as significant; One-Way ANOVA: Post Hoc-Tukey test was applied to compare mean value of *Bcl2* expression pattern between all groups; PMT: Permethrin; NAC: N-Acetylcysteine.

Table 5. Fold change ratio of the *Caspase 9* expression in each group.

	Fold-change ratio	Up-/down-regulation	p-value
PMT vs. control	6.36	Up-regulated	<0.001
NAC + PMT vs. control	2.02	Up-regulated	0.003
Q10 + PMT vs. control	1.72	Up-regulated	0.047
PMT vs. NAC + PMT	3.15	Up-regulated	<0.001
PMT vs. Q10 + PMT	3.70	Up-regulated	<0.001
NAC + PMT vs. Q10 + PMT	1.17	Up-regulated	0.73

Note: $^{*}p < 0.05$ is considered as significant; One-Way ANOVA: Post Hoc-Tukey test was applied to compare mean value of *Caspase 3* expression pattern between all groups; PMT: Permethrin; NAC: N-Acetylcysteine.

Table 6. Fold change ratio of the *P53* expression in each group.

	Fold-change ratio	Up-/down-regulation	p-value
PMT vs. control	4.67	Up-regulated	<0.001
NAC + PMT vs. control	1.85	Up-regulated	0.012
Q10 + PMT vs. control	2.13	Up-regulated	0.001
PMT vs. NAC + PMT	2.52	Up-regulated	<0.001
PMT vs. Q10 + PMT	2.19	Up-regulated	<0.001
NAC + PMT vs. Q10 + PMT	1.15	Down-regulated	0.76

Note: $^{*}p < 0.05$ is considered as significant; One-Way ANOVA: Post Hoc-Tukey test was applied to compare mean value of *Caspase 8* expression pattern between all groups; PMT: Permethrin; NAC: N-Acetylcysteine.

This study examined the healing effects of NAC and Q10 supplementations on histopathological alterations, oxidative stress biomarkers and apoptotic gene expressions in the liver tissue of male rats exposed to PMT. We found that PMT toxicity was conducted by increasing the levels of oxidants and disrupting the antioxidant defense system which finally induced high levels of MDA. Furthermore, PMT significantly caused *bcl2* downregulation, however, enhanced the expression of *Bax, Caspase 3, Caspase 9* and *p53* genes in the liver tissue. Our findings are in consistency with idea that PMT liver toxicity mainly comes from its potential in production of free radicals and encouraging cells towards apoptosis. More recently, Larki *et al.* (2020) evaluated the effect of PMT on histopathological outcomes of liver tissue and the expression of oxidative stress genes, as well as the antioxidant and protective effects of *Echium amoenum*. They found that PMT leads to severe pathological effects in the liver tissue and increased expression of oxidative stress-related genes. Interestingly, *E. amoenum* significantly improved the liver cells protection against PMT and reduced oxidative stress in these cells, similar to our findings. Our results exhibited that PMT not only induces liver tissue injury, but also promotes liver cells apoptosis through enhancing the expression of apoptosis-related genes. In another study, Prater *et al.* (2002) investigated the effect of PMT on thymic cell apoptosis reporting that PMT at a single dose of 1100-1220 mg induced apoptosis of thymic cells. They concluded that PMT leads to severe pathological effects by inducing cell apoptosis. Wang *et al.* (2011) investigated effects of PMT on the production of free radicals and oxidative stress, as well as apoptosis in a mouse model, reporting that PMT induces the production of ROS and oxidative stress in cells. On the other hand, it leads to cell apoptosis, which is probably due to the upraised levels of oxidative stress. Guvenc *et al.*

(2013) reported that PMT elevated the expression of caspase gene in renal tissue cells, which was eventually associated with renal cell apoptosis and severe renal damage. In another study, Kotil *et al.* (2015) examined the effect of PMT on apoptosis and egg cell degeneration in mice reporting that PMT leads to induction of apoptosis and severe degeneration of oocytes in mice. Therefore, these data indicate that PMT has toxicity effects on various tissues or organs and promotes cells apoptosis possibly through the oxidative stress. Based on these observations, using antioxidants or drugs could be an effective strategy for liver protection against PMT-induced toxicity. In the present study, we examined the role of NAC and Q10 in controlling PMT toxicity. Our findings showed that, both Q10 and NAC significantly reduced hepatic cell damage caused by PMT which was associated with the elevated FRAP values and a significant drop in MDA contents. Surprisingly, we found that Q10 and NAC not only improved the total antioxidants capacity, but also mitigated oxidative stress, expression of apoptotic (*Bax, Caspase 3* and *Caspase 9*) and upraised anti-apoptotic (*Bcl2*) mediators. These findings emphasize that both Q10 and NAC can be helpful in management of liver toxicity due to PMT exposure. These findings have been supported by numerous studies that confirmed anti-inflammatory and anti-apoptotic properties of Q10 and NAC (Fuller *et al*. 2006; Fan *et al.* 2017; Sifuentes-Franco *et al*. 2022). The protective effects of NAC and Q10 on cardiac cell, germ cells, rat normal liver cells and Leydig cells were previously documented. Gabbianelli *et al.* (2009) examined the effects of vitamin E and Q10 on myeloperoxidase activity, as well as cell apoptosis in mice receiving PMT. Their results showed that PMT increased the activity of myeloperoxidase, production of free radicals, oxidative stress and ultimately cell apoptosis. However, vitamin E and Q10 n significantly inhibited the pathological effect of PMT and reduced oxidative stress and cell apoptosis. Similarly, Mozhdeganloo *et al.* (2006) assessed the effect of PMT on oxidative stress, and the protective effect of vitamin C supplementation against the toxicity of PMT in rat liver tissue. They reported that PMT significantly elevated the parameters of oxidative stress and lipid peroxidation in rat liver tissue, while vitamin C significantly inhibited oxidative stress and the level of lipid peroxidation biomarkers in it, which was in line with our findings. In accordance with the previous reports and our findings, PMT imposes its detrimental effects on the liver tissue mainly by inducing free radical's formation and triggering extrinsic and intrinsic apoptosis. Since Q10 and NAC are widely approved for their antioxidant effects, they can be considered for their supportive effects in managing PMT toxicity.

CONCLUSION

To sum up, this study clarified that PMT can strongly affect hepatocellular hemostasis mainly by elevating of reactive oxygen species and encouraging of cell death pathway. On the other side, it was found that Q10 and NAC can protect liver tissue by elevating FRAP values, adjusting oxidative stress, as well as down-regulating apoptotic genes.

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