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Protective role of curcumin on hepatic damage methomyl-induced in rats

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Methomyl (Met) is a widely used carbamate pesticide worldwide. Environmental and occupational exposure to methomyl can cause serious health problems. This study was conducted to determine the possible hepatic toxic effects of methomyl in rats. It is also aimed to contribute to understanding the therapeutic potential of curcumin, a natural antioxidant, against this toxic effect in this study. For this purpose, curcumin (100 mg kg^{-1} bw), methomyl (0,8 mg kg^{-1} bw), methomyl + curcumin were given to rats with oral route for 28 days. Alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST) and lactate dehydrogenase (LDH) and total protein, albumin, triglyceride, total cholesterol levels in serum and malondialdehyde level (MDA) and activities of antioxidant enzyme (GPx, GST, SOD, CAT) and histopathological alterations in liver tissue were studied. Methomyl caused significantly increment in the AST, ALT, ALP, LDH activities and total cholesterol and MDA levels. However, methomyl induced importantly reducing in the total protein, albumin, triglyceride levels and SOD, CAT, GPx and GST activities. In addition to, degeneration of hepatocytes, congestion and mononuclear cell infiltration in the liver tissue of methomyl-received rats. In addition, co-administration of curcumin with methomyl importantly reduced the toxicity methomyl-caused on the liver function parameters, lipid peroxidation and activities of antioxidant enzyme and histological structure of liver tissue. The results showed that curcumin significantly may alleviate methomyl-induced hepatoxicity in rats.

Keywords: Histopathology, Liver toxicity, Oxidative stress, Pesticides, Rats

Pesticides are chemicals used to control pests in agriculture and health practices. They are important environmental pollutants[1]. Exposure to pesticides induces harmfull effect on non-target organisms such as birds, fish and mammals[2].

Methomyl is a carbamate group pesticides and it is commonly used in agriculture[3]. US Environmental Protection Agency (US EPA) classified methomyl as highly toxic to humans by oral route, moderately toxic by inhalation route, and indistinctly/slightly toxic by dermal route[4]. Methomyl mainly inhibits vital enzyme acetylcholinesterase, thus it causes nervous system dysfunctions[5]. Methomyl also caused toxic effects in other organs such as kidney and reproductive organs[6-8]. In previous studies, methomyl exposure inhibited the activity of mixed-function oxidases as well as reducing the content of cytochrome P450. These alterations can elevate the sensitivity of cells to reactive oxygen species (ROS). Pesticides induce overproduction of ROS, which act an important role in the pesticides toxicity[9]. Also, pesticides affect the antioxidant levels and the activity of ROS scavenging enzyme system. Methomyl leads to oxidative stress[10].

Oxidative stress can be decreased by natural or synthetic antioxidant substances. Curcumin, a natural polyphenolic antioxidant derived from *Curcuma longa* rhizome, behaves as a free radical scavenger and inhibiting lipid peroxidation. Also, it improves the antioxidant enzyme activities[11,12]. Curcumin has a preservative effect on organ toxicity caused by pesticides and other environmental pollutants[2,13]. Earlier studies showed that various natural and synthetic antioxidants extenuate methomyl-caused toxicity[14,15]. However, there is no research on the potential preventative effect of curcumin on methomyl-caused hepatic toxicity in male rats. The aim of this study was to investigate the possible toxic effect of methomyl on the liver tissue of male rats and whether curcumin supplementation has a protective role on this possible toxic effect. To achieve this purpose, rats were orally exposed to methomyl and/or curcumin for 28 days. ALP, AST, ALT, LDH, total protein, albumin, triglyceride, total cholesterol levels were measured to evaluate hepatic function in serum. MDA levels and antioxidant enzyme activities such as SOD, CAT, GPx and GST were evatuated for the measurement of oxidative stress in the liver tissue. However, histopathological examinations were carried out in liver tissue.

Materials and Methods

Chemicals, animals, experimental design and tissue sampling

Curcumin [Curcumin from *Curcuma longa* (Turmeric) (prutity % ≥77)], methomyl

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Table 1 — Groups of rats in the study

Groups	Treatment (via oral gavage)	Doses (daily)
Group 1	Distilled water	1.0 mL/kg bw
Group 2	Olive oil	1.0 mLkg bw
Group 3	Curcumin	100 mL/kg bw (in olive oil)
Group 4	Methomyl	0,8 mL/kg bw (in distilled water)
Group 5	Methomyl+curcumin	0, 8 mL/kg bw + 100 ml/kg bw

(prutity % ≥98) were provided by Sigma-Aldrich. This study was carried out on thirty adult male albino Wistar rats (200-300 g) from the Gazi University Laboratory Animals Growing and Experimental Research Center. Rats were housed at 22 ± 3°C, and in 12 h light/12 h dark period at metal cages and were given standard rat diet and drinking water during the experimental period. All procedures were ratified by Gazi University Committee on the Ethics of Animal Experimentation (G.U. ET – 17.063).

The rats were divided into 5 groups. There were 6 rats in each group (Table 1). The all chemicals were given *via* oral gavage to rats in the morning hours for 28 days. Methomyl was used oral 1/25 LD_{50} dose for this research[3]. The dose of the curcumin was decided taking into account previous studies[16]. Groups were formed randomly from the rats, each experimental group including 6 rats. The groups in the study and the applications made to the groups are summarized in the Table 1. At the end of experimental period, all rats were weighed and sacrificed under I.M. anesthesia [(ketamine 45mg/kg) + xylazin (5 mg/kg) mixture]. Blood samples were taken from rats *via* intracardiac puncture into sterile tubes to evaluate various hepatic function indicators (ALP, ALT, AST, LDH, total protein, albumin, triglyceride, total cholesterol levels). Liver tissues were rapidly excised for histological examination and assessment of MDA level and activities of SOD, CAT, GPx, GST.

Evaluation of liver weights

After rats were euthanatized at the end of 28th day, liver tissues immediately were isolated and weighed. Relative organ weight was calculated with the formula

$$\text{Relative organ weight}(\%) = \frac{\text{Absolute organ weight}}{\text{Final body weight}} \times 100$$

Evaluation hepatic function parameters

Blood samples collected from the heart were centrifugated and the serum was separated. Levels of total protein, albumin, AST, ALT, ALP, LDH, triglyceride, total cholesterol were analysed in this serum with commercial kits spectrophotometrically by Roche Cobas C501 autoanalyzer.

Evaluation of oxidative stress

The liver tissues taken from dissected rats were homogenized with a homogenizer (Heidolph Silent Crusher M) and then centrifuged. MDA level and activities of antioxidant enzyme in liver tissue samples were measured with a UV spectrophotometer (Shimadzu UV 1700, Kyoto, Japan). The MDA level was measured according to Ohkawa *et al*.[17] method at 532 nm. MDA level was calculated as nmol/mg protein. Hepatic SOD activity was evaluated with the procedure of Marklund & Marklund[18]. Activity of SOD was calculated as U/mg protein. The CAT activity of hepatic supernatant samples was assayed with Aebi's method[19]. The hepatic CAT activity was assigned as mmol/mg protein. The activity of hepatic GPx was evaluated using H_2O_2 as substrate according to Paglia & Valentine method[20]. The activity of hepatic GPx was presented nmol/mg protein. The hepatic GST activity was determined with Habig *et al*. method[21]. The GST activity was calculated as nmol/mg protein. The protein content of the hepatic tissues was analyzed using Lowry *et al*. procedure[22].

Histological investigation

Fixation process of liver tissues was carried out in 10% formalin. Then the tissue samples were dehydrated in the rising grades of alcohol and embedded in paraffin. Paraffin sections (3-6 µm thicknesses) were stained with hematoxylin and eosin (H&E). The liver slides were investigated and photographed by a Olympus LC30 model digital camera attached to a light microscope (Olympus CX43).

Statistical analysis

Statistical analysis was performed with SPSS (Version 18). All data were evaluated for normality using Shapiro-Wilk test and they were found to be normally distributed. To compare different experimental groups were used one-way ANOVA,

Table 2 — Effects of 28 days treatment of methomyl and curcumin on body weight, absolute and relative liver weights in rats

Groups	Absolute liver weight (g)	Relative liver weight (%)
Group 1	9.68±1.19	3.42±0.57
Group 2	9.42±1.08	3.43±0.42
Group 3	8.12±0.62	3.04±0.33
Group 4	11.96±1.99[a,b,c]	4.54±0.8 [a,b,c]
Group 5	11.84±1.05[a,b,c]	4.52±0.2 [a,b,c]

[Values are means ± S.D. for six rats in each group. Significance at P <0.05. [a] Comparison of group 1 and other groups; [b] Comparison of group 2 and other groups; [c] Comparison of group 3 and other groups]

Table 3 — Effects of 28 days treatment of methomyl and curcumin on total protein, albumin, AST, ALT, ALP, LDH, triglyceride and total cholesterol concentrations in serum of rats

	Group 1	Group 2	Group 3	Group 4	Group 5
Total protein (g/dL)	8,16 ±0,28	7,86±0,26	8,21±0,26	5,9±0,27[a,b,c]	7,06±0,14 [a,b,c,d]
Albumin (g/dL)	5,66±0,18	5,5 ±0,16	5,76±0,10	3,58±0,21[a,b,c]	4,41±0,69[a,b,c,d]
AST (IU/L)	92,33±30,2	82,83±22,57	84,33±12,24	163,83±17,46[a,b,c]	110,23±37,30[a,b,c,d]
ALT(IU/L)	54,5±13,75	44,83±9,10	52,66±7,33	96,50±9,81[a,b,c]	72,6±6,87[a,b,c,d]
ALP(IU/L)	90±9,03	89,5±9,02	89,16±15,11	164±12,75[a,b,c]	122,83±14,07[a,b,c,d]
LDH (IU/L)	290±36,7	284,50±61,71	264±38,946	555±65,03[a,b,c]	390,16±80,19[a,b,c,d]
Triglyceride (mg/dL)	86,33±12,97	85,00±16,34	85,66±14,78	40.83±7,38[a,b,c]	62.17±7.93[a,b,c,d]
Total cholesterol (mg/dL)	31,33±6,77	26,33±7,60	30,66±7,60	81±6,60[a,b,c]	64,16±16,59[a,b,c,d]

[[a] Comparison of group 1 and other groups; [b] Comparison of group 2 and other groups; [c] Comparison of group 3 and other groups; [d] Comparison of group 4 and other groups]

followed by Tukey's procedure for multiple comparisons. The all data were expressed as the mean ± Standart Deviation (SD). P value ≤ 0.05 was accepted to be statistically significant.

Results and Discussion

No significant change occurred between the control groups and the curcumin group in terms of all parameters examined.

General health and liver weight

Mortality were not seen in any rats throughout the experimenal period. However, absolute and relative liver weights enhanced in methomyl-intoxicated rats. Curcumin supplementation did not have a protective effect on the enhanced absolute and relative liver weights (Table 2).

Assesment of hepatic function parameters in serum

When the methomyl and methomyl+curcumin groups were compared with the control groups, AST, ALT, ALP, LDH and total cholesterol in the methomyl-intoxicated groups increased. However, an important decline in the total protein, albumin and tryglyceride levels was determined due to methomyl-exposure as compared to control. AST, ALT, ALP, LDH and total cholesterol importantly declined and total protein, albumin and tryglyceride levels statistically significantly elevated in methomyl+curcumin group compared to methomyl group (Table 3).

Assesment of hepatic oxidative damage parameters in liver tissues

A decrease SOD, CAT, GPx and GST activities in the liver tissues of methomyl-intoxicated rats compared to control groups, as well as a significant increase in MDA level were detected. However, SOD, CAT. GPx and GST enzyme activities significantly elevated and MDA level significantly decreased when methomyl+curcumin-group was compared with the methomyl-group (Table 4).

Histopathological evaluation in liver tissues

A normal hepatic architecture in the control, olive oil and curcumin-exposured rats observed in microscopic investigations. Enlargement of sinusoids, degeneration of hepatocytes, congestion, oedema and mononuclear cell infiltration were detected in the liver tissues of methomyl-intoxicated rats. Curcumin supplementation lead to a decrease in the histopathological changes. The congestion and degeneration of hepatocytes observed methomyl+ curcumin-treated rats (Fig. 1A-F).

Methomyl is an insecticide that is widely used in the world. It is highly toxic, especially as it converts

Table 4 — Effects of 28 days treatment of methomyl and curcumin on MDA level and SOD, CAT, GPx, GST activities in the liver tissues of rats

	Group 1	Group 2	Group 3	Group 4	Group 5
MDA (nmol/mg protein)	0.66±0.1	0.65±0.12	0.68±0.09	1.35±0.14[a,b,c]	1.02±0.12[a,b,c,d]
SOD (U/mg protein)	20.55±2.43	19.24±2.95	19.77±2.00	10.31±2.07[a,b,c]	14.58±2.21[a,b,c,d]
CAT (mmol/mg protein)	4.23±1.05	4.16±0.91	3.98±1.05	1.05±0.2[a,b,c]	2.49±0.24[a,b,c,d]
GPx (nmol/mg protein)	8.36±0.71	9.21±0.73	8.50±0.55	3.77±0.42[a,b,c]	5.36±0.51[a,b,c,d]
GST (nmol/mg protein)	67.89±8.21	63.67±7.79	69.96±10.36	29.04±5.71[a,b,c]	46.91±6.99[a,b,c,d]

[Values are means ± S.D. for six rats in each group. Significance at P <0.05. [a] Comparison of group 1 and other groups; [b] Comparison of group 2 and other groups; [c] Comparison of group 3 and other groups; [d] Comparison of group 4 and other groups]

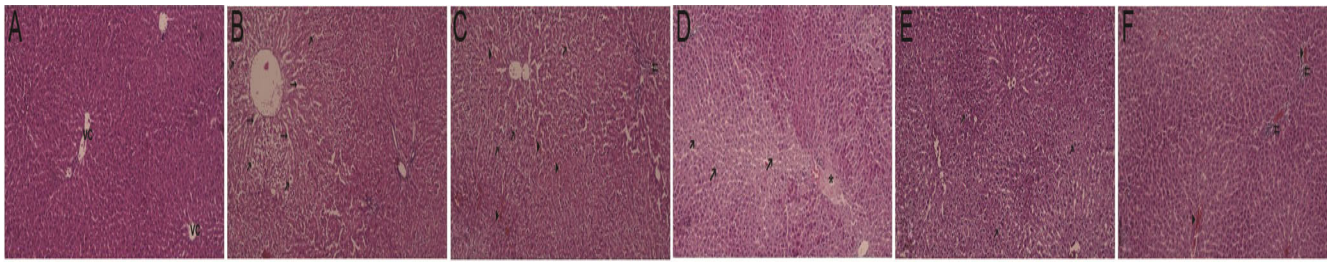

Fig. 1 — (A) Liver sections of methomyl-untreated rats (distilled water-, olive oil-, curcumin-treated rats): Vena centralis (VC), (B) Liver section of methomyl-treated rats: Degeneration of hepatocytes (↗), Enlargement of sinusoids (⇢), (C) Liver section of methomyl rats: Congestion (▶), Degeneration of hepatocytes (↗), Mononuclear cell infiltration (⇉), (D) Liver section of methomyl rats: Degeneration of hepatocytes (↗), necrosis (▶), (E) Liver section of methomyl rats: Degeneration of hepatocytes (↗), (F) Liver section of methomyl + curcumin rats: Mononuclear cell infiltration (⇉), Congestion (▶), ×200 H&E.

to acetonitrile and cyanide by microsomal detoxification enzymes in the liver[23]. This study was conducted to assay the effects of methomyl on some biochemical parameters and histological structure in the liver tissues of rats and to test the possible curative effect of curcumin against methomyl-hepatotoxicity. The evaluation of organ weights is one of the basic indicator for the assessment of organ-toxicity[24]. In this investigation, absolute and relative liver weights significantly enhanced in methomyl-intoxicated rats. An elevated relative liver weight of methomyl-intoxicated rats was also reported in the earlier studies[25].

Carbamate-group insecticides such as methomyl induced oxidative stress in various tissues by causing excessive free radical production and changing free radical scavenging enzyme activity[26]. Oxidative stress is reported as one of the major causes that negatively affect human health[27]. In this investigation, methomyl led to an elevate in MDA level in liver tissues of rats. This result is consistent with the results of previous examinations[26]. MDA is a major products of polyunsaturated fatty acids degredation in the cell membrane[28]. Elevated MDA level is a significant bio-indicator of lipid peroxidation[24]. Lipid peroxidation is one of the molecular mechanisms that cause cell damage in pesticide intoxication. Elevated lipid peroxidation levels induce impaired membrane function and integrity and also alterate in membrane permeability. However, it causes inhibition of membrane-bound enzymes[29]. In this examination, elevation in MDA level is a bio-indicator of lipid peroxidation caused by methomyl. It is possible to say that the increased MDA level is caused by the oxidation of polyunsaturated fatty acids in the membranes caused by methomyl or its metabolites.

There is a dynamic balance between ROS formation and the enzymatic antioxidant defense system during normal physiological conditions. Pesticides can disrupt this balance by causing the formation of excess reactive oxygen species and cause oxidative damage to organisms[30]. Antioxidant defense system enzymes contribute to the detoxification of ROS from the cell, thereby reducing the damage caused by oxidative stress[2].

Endogen defense system enzymes such as CAT,

SOD, GST and GPx have protective properties against cellular oxidative damage lead to by ROS[31]. In present study showed that methomyl lead to a important decline in GPx, SOD, CAT and GST activities in liver tissues of rats. This study of results agree well with the Mansour & Mossa[32] and Chanabe *et al*.[28] studies. Methomyl is an inhibitor of enzymes such as SOD and GST, which catalyze the elimination of ROS[15].

CAT and SOD are the primary defense enzymes against ROS caused by toxic substances[32]. SOD protects tissues and cells from oxidative damage by converting harmful superoxide radicals into molecular oxygen and H_2O_2. CAT and GPx catalyze the breakdown of H_2O_2 to H_2O and protect the cell from oxidative damage of hydrogen peroxide[31]. Thus, H_2O_2, which is formed as a result of the scavenging activity of SOD, is removed from the cells by CAT and GPx. GST, the multi-functional detoxifying enzyme, facilitates its excretion by converting xenobiotics together with GSH into N-acetyl cystine S-conjugates[33]. The reduction in GST activity contributes to the damage of methomyl exposure. In the study, the decrease in SOD, CAT and GPx activity leads to enhanced in superoxide radicals and the level of H_2O_2, thereby causing oxidative damage. The reduction in CAT, GPx, GST, and SOD activities and elevated MDA levels may reflect excessive ROS production caused by methomyl exposure.

The main organ involved in the detoxification procedure of pesticides is the liver. For this reason, the liver is the organ that is exposed to pesticides and toxic metabolites at the maximum level[34]. Serum enzymes such as ALP, ALT, AST and LDH are mainly used in the evaluation of hepatic function disorders and liver injury[35]. In earlier study showed that pesticides induced elevation of ALP, ALT, AST and LDH activities[36]. These enzymes are mainly localized in the cytoplasm and are secreted into the blood when hepatocyte cell membranes are damaged, thus increasing serum levels[37]. This study showed an important increase in hepatic marker enzymes (AST, ALP, ALT and LDH) in methomyl-intoxicated rats. This increase in hepatic enzymes can be explained by the increase in membrane permeability due to lipid peroxidation of hepatocyte membranes caused by methomyl and the circulatory leakage of these enzymes. In addition, high ALP levels can result from impaired bile duct function. Serum ALP level may increase due to elevated bile pressure and presence of cholestasis[38]. However, lipid and protein metabolism alterations are also used to evaluate hepatic structure and function[31]. In the present study, it was found that there was an important enhance in the total cholesterol level of methomyl-treated rats. Elevated total cholesterol levels can be a sign of hepatic damage. This increase may be due to the adverse effect of methomyl on the permeability of the cell membrane, as well as the obstruction of the bile ducts, which stops or decreases the secretion of cholesterol into the duodenum. It has been reported that insecticides cause a reduction in triglyceride levels[33]. Parenchymal liver disorders are associated with a decline of triglyceride levels. In this study, methomyl caused a statistically significant decrease in triglyceride level. In addition, there was a decrease in albumin and total protein levels in rats exposed to methomyl. Albumin is produced by hepatic cells and pesticides can reduce the production of albumin. It is likely that methomyl leads to changes in amino acid and protein synthesis and metabolism. These results are consistent with the presence of hepatic cell damage seen with microscopy and earlier studies[39].

Methomyl induced histopathological alterations in reproductive and gastrointestinal system organs[3,26]. In this study, methomyl exposure induced histopathological alterations in liver tissue such as mononuclear cell infiltration, necrosis, dilatation of sinusoids and congestion. It is possible to say that these histopathological changes are caused by significantly increased hepatic lipid peroxidation, decreased antioxidant defense system enzymes and thus oxidative damage. Histological and biochemical findings obtained from this study support each other.

Toxicity of pesticides-caused are reduced by natural antioxidants such as curcumin[1,12]. Previous studies showed that curcumin provides protection against the toxic effects of pesticides and some environmental pollutants[40-42]. In this study, curcumin supplementation led to a significant decrease in MDA level, which was increased due to methomyl exposure, and a statistically significant increase in decreased antioxidant enzyme activities. Curcumin is an antioxidant that has free radical scavenging activity. Curcumin can prevent lipid peroxidation, mainly through its binding ability, and protect the cell membrane from oxidative damage[42]. However, curcumin indirectly induces the expression of genes of antioxidant enzymes such as SOD, CAT, GPx[43]. It is a potential Nrf2 activator with therapeutic properties against oxidative stress[44]. Nrf2 is a

transcription factor and resides in the cytosol. NFR 2 controls the expression of genes encoding antioxidant defense proteins. It is translocated into the nucleus in response to excess ROS production[45]. This location change causes an increase in the transcription of antioxidant genes and anti-inflammatory genes[46]. Thus, curcumin can protect against hepatic oxidative damage by its free radical scavenging property and by increasing Nrf2 and antioxidant defense enzyme expression and activity by curcumin. In this study, curcumin supplementation reduced the histopathological changes and liver dysfunction caused by methomyl.

Conclusion

In conlusion, methomyl caused hepatic damage, as evidenced by changes in hepatic function parameters in serum, histological structure and oxidative stress markers. However, curcumin supplementation, probably through enhanced cellular antioxidant defence, alleviatedthe methomyl-toxicity in liver tissues. As a result, curcumin can be recommended as a potential ameliorative against the toxicity caused by methomyl.

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Conflict of interest

The authors declare no conflict of interest.

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