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ORIGINAL ARTICLE

Carvacrol Attenuates Disrupted Lipid Profile Induced by Organophosphates in Male Wistar Rat: a Comparative Toxicity

Ali Salari[1], Kambiz Roshanaei[2], Bahram Rasoulian[3], Javad Khalili Fard[*4,5]

[1] *Department of Physiology, Faculty of Sciences, Qom Branch, Islamic Azad University, Qom, Iran*

[2] *Department of Biology, Faculty of Sciences, Qom Branch, Islamic Azad University, Qom, Iran*

[3] *Hepatitis Research Center, Lorestan University of Medical Sciences, Khorramabad, Iran*

[4] *Razi Herbal Medicines Research Center, Lorestan University of Medical Sciences, Khorramabad, Iran*

[5] *Department of Pharmacology and Toxicology, Faculty of Pharmacy, Tabriz University of Medical Sciences, Tabriz, Iran*

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KEYWORDS

Malathion;
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ABSTRACT: Many people in agricultural industry are nowadays struggling with protecting their products utilizing pesticides. Pesticides, such as organophosphate (OPE) insecticides, may remain on agricultural products as pesticide residues. Malathion (MTN) is an OPE widely used around the world. Some OPEs, such as parathion (PTN), are more toxic pesticides and have been restricted. Carvacrol (CRL) is a major component of *Satureja khuzestanica* essential oil, which exerted protective effects against toxicity of chemicals. OPEs can alter lipid profile. In addition, lipid profile may alter due to certain disorders, such as nephrotic syndrome. The present study aimed to investigate the effects of coadministration of CRL and the effect of these two pesticides on serum acetylcholinesterase (AchE) activity and lipid profile in male wistar rat. Coadministration of CRL and PTN, but not MTN, significantly decreased serum AchE activity in comparison with the group receiving OPES. Serum levels of cholesterol and triglyceride were analyzed after 10 days of administration of the chemicals. Malathion and PTN significantly increased cholesterol and triglyceride. However, administration of CRL modified lipid profile ($P < 0.05$). It was concluded that CRL could be considered as a drug to treat lipid profile alteration and owing to the beneficial effects as well as inhibition of acetylcholine, it could be considered as a component of OPE pesticide.

INTRODUCTION

Insecticides, such as OPEs, are pesticides being widely used throughout the world to control green flies, harvest bugs, and other insects. Nowadays, OPEs are increasingly applied in agriculture and as household pesticides. Pesticides residue in food products, such as vegetables, which is a major concern because of chronic exposure [1]. Maternal exposure to OPEs could adversely affect prenatal development [2]. OPE exposure leads to cholinergic crisis due to inhibition of enzyme AchE. MTN is a common OPE insecticide used for pest control. This compound exerts various adverse effects, such as renal and hepatic disorders [3]. Nephrotic syndrome is associated with hyperlipidaemia. Lipids and lipoproteins profile disruption are characteristics of patients with nephrotic syndrome.

*Corresponding author: khalilifardardalij@tbzmed.ac.ir (J. Khalili Fard)
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Nephrotic syndrome increases serum concentrations of LDL-C, total cholesterol, as well as triglyceride and decreases HDL-C. Patients with nephrotic syndrome have disrupted lipid and lipoprotein metabolism, which makes these patients at risk for cardiovascular disease. Moreover, in children with nephrotic syndrome without renal failure, the increase in serum lipoprotein (a) levels is associated with hypoalbuminemia, which stimulates hepatic Apolipoprotein B synthesis and is not associated with proteinuria. Nephrotic syndrome may ensue after exposure to MTN [4]. Thus, it could be proposed that lipids and lipoproteins profile disruption is associated with OPE exposure.

PTN is restricted in various countries because of its severe toxicity. It could cause liver, heart, and renal dysfunction via metabolism to paraoxon [5-7]. This compound has been restricted in certain countries, but other countries, such as South Africa, import it under specified circumstances [8]. It has been reported that OPEs, like MTN, may exert genotoxicity which is reduced by CRL [9].

MTN exposure has been associated with kidney injury. MTN also diminishes antioxidant enzymes activity. Catalase, superoxide dismutase, and glutathione peroxidase are affected by MTN, leading to malondialdehyde production in both liver and kidney. On the other hand, liver and kidney impairment, induced by chronic exposure to MTN, attenuates by coadministration of antioxidants [10]. It has been reported that some herbal components attenuates the impairment induced by OPE, such as MTN. Among them, taurine, resveratrol, and crocin alleviated toxicity of MTN mainly owing to their antioxidant effects [11-13]. Thus, natural components of herbal plants with antioxidant effects could be suitable choices for declining the oxidative stress induced by OPEs.

CRL is a water insoluble monoterpene found in the essential oil of *Satureja rechingeri*, *Satureja thymbra*, and many other herbal plants [14]. One of the major effects of some monoterpenoid and sesquiterpenes are inhibition of acetylcholinesterase. CRL changes acetylcholinesterase activity [15]. CRL can inhibit acetylcholinesterase more effectively than some other monoterpenoid. The use of OPEs with CRL might have several complexities, including cholinergic crisis. CRL can inhibit acetylcholinesterase more effectively than some other monoterpenoid [16-18]. CRL has shown many other beneficial impacts, such as antioxidant and anti-inflammatory effects. It can lower triglyceride levels [19]. Recently, the effects of CRL on MTN- and PTN-induced nephrotoxicity have been investigated. MTN and PTN administration has been found to induce inflammation in kidney tissue in comparison with control. CRL improves inflammation in comparison with MTN and PTN group. Moreover, CRL loaded Beta Cyclodextrin-Alginate-Chitosan-based Nanoflowers attenuates renal toxicity induced by MTN and PTN. Meanwhile, the effects of MTN and PTN on triglycerides and cholesterol still remain unclear.

Considering the anticholinergic effect of OPEs, concomitant exposure to CRL containing herbs and this type of pesticides may lead in numerous complexities. OPEs can induce nephrotic syndrome which is associated with hyperlipidemia. On the other hand, CRL could have lipid-lowering effects. Therefore, this study was conducted to investigate the effects of coadministration of CRL with MTN and PTN on lipid profile.

MATERIALS AND METHODS

Materials

MTN and PTN were obtained from Sigma-Aldrich (United States). CRL (96%) was obtained from Razi Herbal Medicines Research Center (Iran). Other chemicals were obtained from Merck Chemical Co. (Germany).

Animals

The animals were obtained from Pasteur Institute, Tehran, Iran, and kept in dark/light cycles of 12h/12h in an air-conditioned room (22-25°C), with free access to standard chow and water. There were seven male wistar rats in each group. Animal care followed the procedures by the Ethics Committee of Lorestan University of Medical Sciences, Lorestan, Iran. The rats received 25 mg kg^{-1} CRL, 0.3 mg kg^{-1} MTN, 0.004 mg kg^{-1} PTN from day 1 to day 10.

Doses of pesticides were according to the guidelines of World Health Organization for drinking-water quality.

Collection and preparation of samples

In the morning of the 11th day, after anesthetizing, the animals were sacrificed. Subsequently, their blood samples were collected and serums were separated for analyzing cholesterol and triglyceride.

Biochemical assay

Serum levels of AchE were determined using ELISA kits. Cholesterol and triglyceride were also determined using available kits (Parsazmun, Tehran, Iran).

Statistical analysis

All the data in this study were analyzed via SPSS 16 using one-way ANOVA followed by Tukey post-hoc test and were expressed as mean ± SD. Significant differences were established once $P < 0.05$.

RESULTS

Serum cholesterol

To evaluate the impact of CRL on MTN and PTN-induced hyperlipidemia, serum levels of the nephrotic syndrome marker cholesterol (Figure 1) was determined. Administration of 0.3 mg kg^{-1} MTN and 0.004 mg kg^{-1} PTN for 10 days significantly ($P < 0.05$) increased serum cholesterol in comparison with the control. Coadministration of 25 mg kg^{-1} CRL and MTN, as well as PTN, showed a significant ($P < 0.05$) improvement in the levels of serum cholesterol in comparison with the MTN and PTN groups. Surprisingly, CRL did not improve serum levels of cholesterol in group MTN ($P < 0.05$).

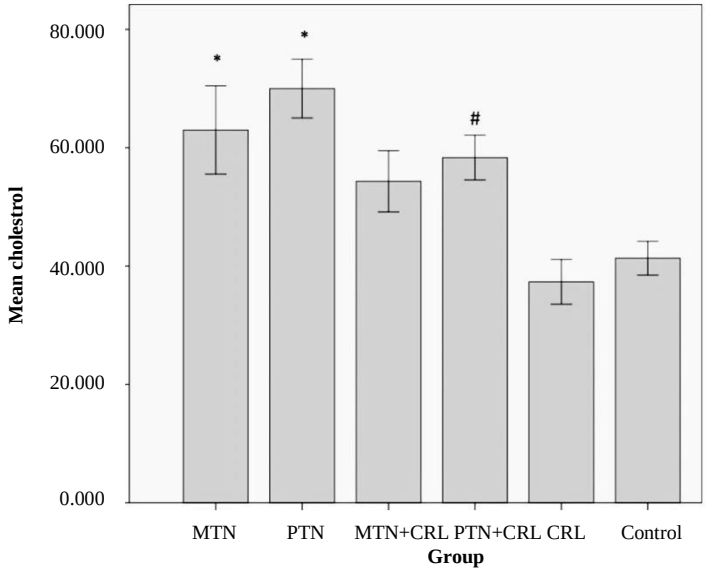

Figure 1. Serum levels of cholesterol. CRL modified serum levels of cholesterol of the groups receiving PTN ($P < 0.05$).
* significant difference between the group and control ($P < 0.05$)
# significant difference between the group and the one receiving PTN ($P < 0.05$)

Serum triglyceride

To evaluate the impact of CRL on MTN and PTN-induced hyperlipidemia, serum levels of the nephrotic syndrome marker triglyceride (Figure 2) was determined. Administration of 0.3 mg kg^{-1} MTN and 0.004 mg/kg PTN for 10 days significantly ($P < 0.05$) increased serum triglyceride in comparison with the control. Coadministration of 25 mg kg^{-1} CRL and MTN, in addition to PTN, showed a significant ($P < 0.05$) improvement in

the levels of serum triglyceride in comparison with the MTN and PTN groups. CRL improved the serum levels of triglyceride in the MTN and PTN groups ($P < 0.05$).

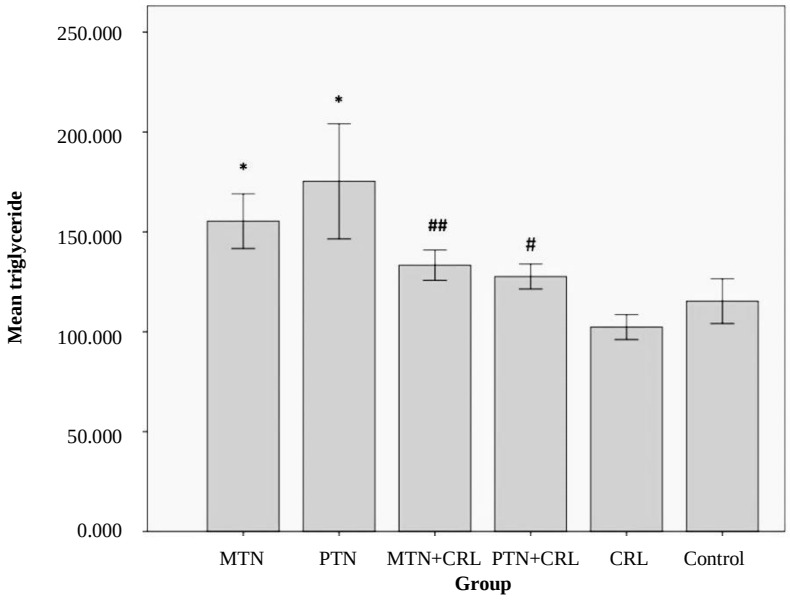

Figure 2. Serum levels of triglyceride. CRL modified serum levels of triglyceride of the groups receiving MTN and PTN ($P < 0.05$).
* Significant difference between the group and the control ($P < 0.05$)
# Significant difference between the group and the one receiving PTN ($P < 0.05$)
Significant difference between the group and the one receiving MTN ($P < 0.05$)

Serum AchE activity

To evaluate the impact of CRL on MTN and PTN, serum AchE activity (Figure 3) was determined. Administration of 0.3 mg kg^{-1} MTN and 0.004 mg/kg PTN for 10 days significantly ($P < 0.05$) decreased serum AchE activity in comparison with the control. Coadministration of 25 mg kg^{-1} CRL and PTN showed a significant ($P < 0.05$) decrease in serum AchE activity in comparison with the PTN group ($P < 0.05$).

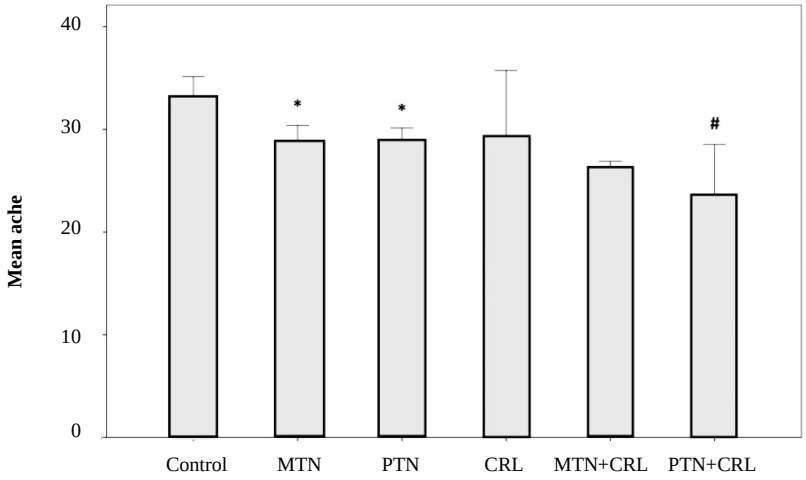

Figure 3. Serum AchE activity. CRL decreased serum AchE activity of the groups receiving PTN ($P < 0.05$).
* Significant difference between the group and control ($P < 0.05$)
# Significant difference between the group and the one receiving PTN ($P < 0.05$)

DISCUSSION

Approximately 5.6 billion pounds of pesticides is used annually around the world and about 1.8 billion workers around the world are involved in agriculture, which plays an important role in regional economy [20]. Although traditionally agriculture is responsible for providing food and fiber, agriculture is nowadays involved in producing row materials for herbal medicines [21, 22]. On account of the increasing world population, food supply and herbal medicines have become important challenges which have led to increased pesticides production.

Pesticides have exerted several adverse effects in short-term or long-term exposure. Consequently, the contamination of food supply and herbal medicines with hazardous chemicals has been a major concern. Approximately 5.6 billion pounds of pesticides is used annually around the world [20]. Moreover, some pesticides, including OPEs, like MTN, are applied for domestic purposes. Household exposure to OPEs are common and leads to numerous effects on ecosystem, including non-target organisms, such as human being, which are directly and indirectly exposed to these chemicals [23, 24]. Due to direct and indirect exposure to residues of pesticides in food, many studies have been conducted to reduce the undesired harmful effects induced by pesticides.

Adverse health effects caused by chemicals, such as organic solvent, may occur acutely and be readily detectable. They may also result from chronic exposure and have insidious onset. They are primarily dependent on these factors: toxicity of the chemicals, route of exposure, initial concentration, and duration of exposure, individual susceptibility, and interactions with other chemicals.

Depending on the initial concentration, duration of contact, type of chemical, and the target cells, the cellular responses may be minimal and reversible, activating adaptive responses. In higher concentration and/or duration of exposure, the cellular responses may be severe, leading to major changes in the structure and function of target cells, which may cause cell death. Furthermore, regulation of gene expression by chemicals is dictated by the type, quantity, rout, and duration of exposure to chemicals.

In this study, the duration of exposure was 10 days and the rout of exposure to pesticides was intraperitoneally. The effects of concomitant use of CRL on AchE activity and hyperlipidemia induced by MTN and PTN were investigated. According to the obtained findings, PTN exposure for 10 days, with a daily dose of 0.004 mg/kg, disrupted lipid profile, which was confirmed by the results of cholesterol and triglyceride.

As the dose and/or the duration of exposure to MTN and PTN increases, the adverse health effects, such as disrupted lipid profile, may aggravate. In another study, it was revealed that 10 days of exposure to MTN and PTN induces renal impairment [25]. Based on these results, it could be concluded that MTN and PTN exposure leads to nephrotic syndrome since on of the important biomarkers of nephrotic syndrome is disrupted lipid profile.

In vivo and *in vitro* studies have revealed that OPEs could be important carcinogens of breast cancer. PTN and MTN can induce cell proliferation [26, 27]. They can also alter metabolic pathways. PTN exposure induces cytochrome P450 upregulation [28] while MTN inhibits hepatic cytochrome P450 and cytochrome b5 [29]. PTN has shown undesired harmful effects on several organs, such as kidney, liver, and heart [30-32]. PTN-induced adverse effects are mainly attributed to its metabolite paraoxon [33].

Liquid phenolic monoterpenoid CRL is insoluble in water and a major component of the essential oil of some herbs, like *Satureja khuzestanica Jamzad [34]*.

PTN and MTN inhibit AchE and induce cholinergic symptoms. In a previous study, it was concluded that CRL can also inhibit AchE [35]. CRL could not inhibit AchE significantly, but coadministration of CRL with PTN, not MTN, can inhibit AchE more effectively than PTN ($P < 0.05$). Additionally, AchE activity was reported to decrease by coadministration of CRL with MTN rather than MTN alone.

Even though in this study, CRL could not significantly inhibit AchE at this dose, other studies have shown that CRL has inhibitory effects on AchE. Further studies should

be designed to obtain a dose response curve for determining the effect of different doses of CRL on AchE. Obtaining such a response dose curve is conducive to designing an effective formulation including both CRL and OPE against insects.

PTN has induced great changes in lipid metabolism (total cholesterol, triglyceride, very low-density lipoprotein, low-density lipoprotein, and High-density lipoprotein) in fish [36, 37]. MTN exposure has been found to significantly increase the serum levels of alanine transaminase, aspartate transaminase, and cholesterol [38]. In the present study, it was revealed that PTN and MTN exposure during 10 days increases the serum levels of cholesterol and triglyceride. Nephrotic syndrome is characterized by hyperlipidemia. Further experiments should be carried out to investigate renal function and lipid profile changes following the exposure to PTN and MTN.

In a previous study, it was reported that administration of CRL for 21 days improved hypercholesterolemia; it was concluded that CRL shows hepatoprotective and hypolipidemic effects [39]. Furthermore, it has been reported in the previous studies that plants containing CRL can affect lipid profile. *Satureja sahandica Bornm* extract lowers blood cholesterol in broiler chickens [40]. A diet rich in *Satureja khuzestanica Jamzad* significantly increases body weight gain and decreases cholesterol level [41]. In the present work, it was revealed that increased serum levels of cholesterol and triglyceride after exposure to PTN and MTN is alleviated by the use of CRL. Hence, cholesterol- and triglyceride-lowering effects of plants, such as *Satureja* species, could be attributed to CRL.

CONCLUSIONS

CRL may be considered as a remedy for treating hypercholesterolemia. Moreover, considering AchE inhibitory effect of CRL, it could be concluded that the use of CRL in the formulation of OPEs could control pests more effectively than conventional OPE formulations.

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Conflicts of interest

None declared.

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