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Review Article

The Possible Protective Effect of Resveratrol on Diazinon-Induced Oxidative Stress and Hepatic Injury

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Abstract

Diazinon, one of the most known organophosphate pesticides (OPs), has harmful effects on human organs. Acetylcholinesterase inhibition, oxidative stress, and inflammation are the major mechanisms of diazinon toxicity. Diazinon has several toxic effects on the liver. Resveratrol (RES) is a natural polyphenol compound with antitumor, anti-diabetic, anti-obesity, anti-oxidant, anti-aging, and anti-inflammatory effects. This compound can inhibit lipid peroxidation, protein oxidation, and DNA damage. Moreover, it can induce sirt-1, PI3K/AKT, and HO-1 pathways (negative regulators of inflammatory pathways). A large body of evidence indicated that resveratrol can attenuate liver damage by organophosphates. In this short review, we discuss the significant role of this phytoestrogen and antioxidant against the hepatotoxic effect of diazinon as an OP. With elucidation of the role of this supplement in reducing harmful effects of diazinon, it can be used as a protective agent in people at risk of adverse effects of diazinon.

Keywords: Diazinon, Oxidative stress, Inflammation, Liver, Toxicity, Resveratrol

Introduction

Pesticides are materials which are purposefully used in agriculture to increase food production. Organophosphate pesticides (OPs), as one of the most significant pesticides, have been extensively used in past decades (1). Because of the wide availability, the toxicity of OPs is a significant challenge encountered by agricultural and biological environments (2). OP poisoning is recognized as a major health problem and a common hazard in Iran (3). Diazinon (O,O-diethyl-O-[2-isopropyl-6-methyl-4-pyrimidinyl] phosphorothioate), a synthetic chemical substance, is classified as moderately hazardous (class II) organophosphorus insecticide. It has toxic effect on various organs including kidney, liver, heart, and brain, it is noted that other systems including immune and reproductive systems are affected by diazinon (4). It can be absorbed through the digestive system, skin, and respiratory tract when inhaled. Kidney has a major role in diazinon detoxification. Acetylcholinesterase suppression is a major mechanism of diazinon toxicity which leads to the accumulation of acetylcholine, prevention of signal transduction, and irreversible destructive effects on the nervous system. In addition, studies have revealed that oxidative stress could be another important mechanism involved in diazinon toxicity (5,6). Based on many studies, dose, route of exposure, physicochemical properties, and rate of metabolism play an important role in the severity and duration of diazinon poisoning (7). Diazinon is metabolized by hepatic microsomal enzymes to hazardous metabolites such as diazoxon, hydroxyl diazoxon, and hydroxyl diazinon that have harmful effects on different organs. In hepatocytes, cytochrome P450 systems and membrane transport system of mitochondria are affected by diazinon (1). Reactive metabolites of diazinon have major role in increasing free radical production and the depletion of tissue antioxidant has a major role in hepatocellular injury (4). Reactive oxygen species (ROS) and reactive nitrogen species (RNS) formation (4), high level of malondialdehyde (MDA) (8), excessive number of abasic sites of DNA (representative of oxidative DNA damage) (9), reduction of glutathione (GSH), superoxide dismutase (SOD), catalase (CAT) (10) and vitamin C (11) are the most important procedures modulated by diazinon in oxidative stress. The apoptosis and necrosis of hepatocytes result from antioxidant depletion (12).

High levels of liver enzymes including aspartate transaminase (AST), alanine transaminase (ALT), and alkaline phosphatase (ALP), as indicators of liver damage, are reported in diazinon exposure (4). Oxidative stress damages the liver via lipid peroxidation, suppression of B-oxidation enzymes, and fatty acid accumulation in hepatocytes (13). Liver cells including Kupffer, stellate, and endothelial cells are more sensitive to oxidative stress. Kupffer cells can produce several cytokines such as tumor necrosis factor alpha (TNFα). Concerning stellate cells, the proliferation and collagen synthesis of hepatic stellate cells are triggered by lipid peroxidation caused by oxidative stress. Additionally, oxidative stress alters metabolic pathways that control normal biological functions (14).

Organophosphates cause histoarchitectural disturbances in the liver which lead to disturbances in metabolic pathways of lipids, carbohydrates, and proteins. Previous studies indicated that diazinon increases the activity of gluconeogenesis enzymes including glycogen phosphorylase and phosphoenolpyruvate carboxykinase. Moreover, diazinon can alter liver protein metabolism (decrease in total protein and albumin) (15).

Various studies confirmed that hepatotoxicity induced by diazinon is related to inflammation (16). Diazinon increased hepatic expression and serum level of TNF-α (17). OP exposure and the high level of pro-inflammatory cytokines have a close association (16,18).

Diazinon can activate apoptotic pathways in the liver via caspase9 and caspase3 activation, increase in Bax/Bcl2 ratio, suppression of endoplasmic chaperone with anti-apoptotic properties (19,20).

It seems that implementing the supplementation strategy to ameliorate the toxic effect of diazinon may provide public health benefits. It is suggested that various substances stop the harmful effects of diazinon on the liver (21). Many studies investigated bioactive compounds extracted from plants with potential therapeutic effects (22). Plants produce low-molecular-weight secondary metabolites which have important roles in the defence system against infections or stress (23). Among them, resveratrol (RES), as a type of polyphenolic compound and phytoalexin, caught remarkable attention. Several plant species, such as peanuts, pistachios, berries, grapes, and nuts can produce RES (24). Red grape is a rich source of RES, it has been estimated that fresh grape skin contains about 50–100 g of resveratrol/g (25). Adverse conditions such as stress, injury, UV irradiation, and fungal infection can induce ROS generation (26). Pharmacological studies on RES reported anti-oxidant, anti-inflammatory, anti-cancer, anti-aging, anti-obesity, anti-diabetic, cardioprotective, neuroprotective, and anti-microbial properties of RES (27). Furthermore, health benefits of RES were indicated in treating several hepatic disorders including acetaminophen, ethanol, carbon tetrachloride, atherogenic diet induced hepatotoxicity and ischaemia/reperfusion-induced damage of the liver (28).

RES treatment can decrease thiobarbituric acid reactive substances level, increase SOD and CAT activities and inhibit activation of nuclear factor NF-κβ (as a ROS sensitive transcription factor) (29-32). Various investigations confirmed that RES significantly suppresses cell membrane lipid peroxidation, protein oxidation, and DNA damage because it can directly scavenge different free radicals (33,34). RES is an activator of sirtuin-1 (SIRT-1) (35) which has a role in cell survival (via decreasing oxidative stress and improving forkhead box O transcription factors (36). SIRT-1 has an important function in modulating lipid metabolism, oxidative stress, and inflammation in the liver (37).

Anti-inflammatory effects of RES are indicated by direct inhibition of cyclooxygenase-2 activity (38) and reduction of gene expression of inflammatory mediators such as inducible interleukine-6 (IL-6) and interleukine-1 beta (IL-1β) (39).

RES decreases the expression of cytochrome c, Bax, and caspase 3 and restored anti-apoptotic markers to control level (40). RES has genoprotective effect on genotoxicity induced by permethrin (an insecticide) in cultured human lymphocytes (41).

RES plays an important role in metabolic pathways. In vivo studies showed that RES can increase and decrease hepatic expression of enzymes involved in lipolysis and lipogenesis, respectively (42). In addition, RES improves glucose metabolism by increasing insulin receptor substrate 1, glucose transporter type4, peroxisome proliferator-activated receptor α and Ɣ (43).

The hepatoprotective effects of resveratrol against fibrosis (44) and oxidative stress (45) are reported. RES can significantly decrease the expression of fibrosis-related genes including transforming growth factor beta1, collagen type-1, α-smooth muscle actin, and hydroxyproline in rat with dimethylnitrosamine induced liver fibrosis (46). The protective effect of RES against fibrogenesis is mediated by its polyphenol capacity (47).

RES treatment significantly decreased liver damage induced by CCl_4 via suppression of lipid peroxidation, improvement of hepatic GSH depletion (following CCl_4 administration), enhancement of GST activity, and nodule growth inhibition (48).

RES has beneficial effect on hepatic injury after hemorrhage via up-regulation of PI3K/AKT and HO-1 (regulators of various crucial events in the inflammatory response), and modulation of inflammatory cytokines (49).

The ameliorating effect of RES in OPs toxicity was reported. In vitro studies presented that RES can attenuate neurotoxic effects in PC12 cells via suppression of ROS production and enhancement of enzymatic antioxidant systems.

RES reduced the expression of apoptotic markers and restored the expression of anti-apoptotic markers, thereby preserving the PCL2 cells from programmed cell death (40). RES can boost the catalytic activity of Cyp2d22/

CYP2D6 in mice treated with maneb (MB), a fungicide, and paraquat (PQ), a herbicide. These xenobiotic-metabolizing enzymes have protective effects against parkinsonism induced by MB and PQ (50).

Animal model indicated that RES could inhibit the inflammatory response, oxidative stress, and apoptosis induced by paraquat (one of the world's most widely used herbicide). RES significantly declined serum AST and ALT, MDA, and hepatic TNF-α levels and the expression of apoptosis markers (including p53, Bax). In addition, this compound increased anti-apoptotic gene (BCL-2) expression and liver GSH level. Histopathological studies of the liver confirmed these results (51).

The anti-oxidative effect of resveratrol has been indicated in rats treated with glyphosate-based herbicides (GBH) via reducing MDA levels and increasing GSH levels. Moreover, RES minimized liver injury induced by GBH via improvement in biochemical markers such as AST, ALT, and ALP. These changes were reflected in the histopathological assessment of the liver (52).

Malathion is another organophosphate pesticide which significantly increases the level of liver enzymes including ALT, AST, and ALP and damages hepatocytes. In vivo studies showed that RES improved the activity of liver antioxidant enzymes and decreased lipid peroxidation and liver enzymes. Additionally, RES decreased serum nitric oxide level and lipid peroxidation in malathion-treated rats compared to the control group. RES suppresses liver damage by malathion via oxidative stress inhibition (47). RES administration can moderate the genotoxic effect of malathion in the liver by decreasing 8-hydroxyguanosine concentration. RES can improve malathion-induced histopathological changes in the liver (53). Moreover, RES has protective effects on renal damage induced by malathion. This antioxidant can reduce kidney MDA, blood urea nitrogen, nitric oxide levels and improve renal TAC level. Histopathological findings confirm these beneficial effects (54).

Figure 1 shows a summary of the antioxidant effects of RES on hepatotoxicity induced by diazinon.

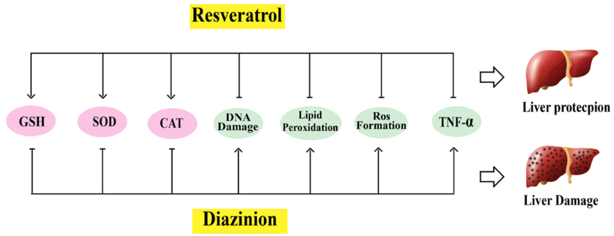

Figure 1. The Possible Effect of Resveratrol on Oxidative Stress and Inflammation Induced by Diazinon in Liver. GSH: glutathione; SOD: superoxide dismutase; CAT: catalase; ROS: reactive oxygen species; TNF-α: tumor necrosis factor α; ⊥: Inhibitory effect; ↑: Stimulatory effect.

Conclusion

Pesticides continue to be a substantial component in modern agriculture to increase the agricultural yield. The use of pesticides in agriculture is inevitable. The application of compounds with various anti-inflammatory, antioxidant, and hepato-protective effects such as RES can decrease the harmful effects of pesticides. In this article, we introduce a critical review of the potential preventive and therapeutic role of RES in liver toxicity induced by diazinon. Regarding the protective effects of RES, it may offer an opportunity to overcome oxidative stress and hepatocellular damage induced by diazinon. Additionally, it may be a novel choice for protection in people at risk of adverse effects of diazinon.

Conflict of Interest Disclosures

The authors declare no conflicts of interest.

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