Int. j. adv. multidisc. res. stud. 2025; 5(1):285-294

Received: 25-11-2024
Accepted: 05-01-2025

International Journal of Advanced Multidisciplinary Research and Studies

ISSN: 2583-049X

Diazinon Properties, Mode of Action, and Toxicological Effects on Non-target Organisms

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DOI: https://doi.org/10.62225/2583049X.2025.5.1.3652
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Abstract

Diazinon (DZN) (O, O-diethyl-O-[2-isopropyl-6-methyl-4-pyrimidinyl] phosphorothioate) is one of the most widely applied organophosphorus pesticides in the livestock industry. It is an anticholinesterase organophosphate insecticide that inhibits the action of acetylcholinesterase, resulting in an abundance of acetylcholine, which affects neuromuscular transmission and causes insect paralysis and death. However, DZN residues in the environment can affect non-target organisms through the air, water, soil, and food chain, which raised worries about its detrimental consequences. Oxidative stress (OS) caused by reactive oxygen species may be the key mechanism that might be related to DZN toxicity. This article provides a comprehensive investigation of DZN's toxicity pattern, with an emphasis on its negative effects on the neurological, hepatic, cardiac, and nephrotic systems, as well as its effects on reproductive processes. It also addresses how DZN affects hormonal levels, causing endocrine disorders. Consequently, identifying these pathways might offer helpful insight on the mechanisms of DZN activity on various tissues. This review aimed to raise awareness about the harmful effects of DZN exposure.

Keywords: Diazinon, Contaminant, AchE, Oxidative Stress, Organs Toxicity

Introduction

Pesticides are a class of chemicals used to eradicate insects, weeds, fungus, and bacteria [1-2]. The use of pesticides in veterinary field is economically required. There are essential to control insects and parasites that impair livestock production, consume crops used for animal feed, and spread illnesses [3]. The vast majority of pesticides used in the veterinary medicine are ectoparasiticides, which target insects that live on animals' skin. Ectoparasiticide active components are commonly applied to animals' skins in a range of formulations [4].

Organophosphates (OPs) pesticides are one of the most frequently used pesticides. They are esters, amides, or thiols derived from phosphoric, phosphonic, phosphinic, or thiophosphoric acids, coupled with two organic groups and a side chain containing cyanide, thiocyanate, or phenoxy groups [5-6]. These pesticides suppress the function of acetylcholinesterase, an enzyme that degrades acetylcholine, a neurotransmitter that controls the nervous system. Organophosphates block acetylcholinesterase, causing acetylcholine buildup that can lead to nervous system overstimulation and, finally, paralysis and death of the target insect [7]. Even with its benefits, its extensive use has killed non-target creatures, contaminated the environment, and caused acute and severe chronic toxicity in many different parts of the world. Thus, it has been considered a health risk to the environment [8].

Among the most popular organophosphate pesticides is diazinon (DZN). It is a popular anti-parasitic medication used to combat external parasites like ticks and mites [9]. The present review will focus on current information about DZN, its physical and chemical properties, and the broad toxicological impacts of DZN, providing insight into the processes behind these effects.

a. Chemical Structure

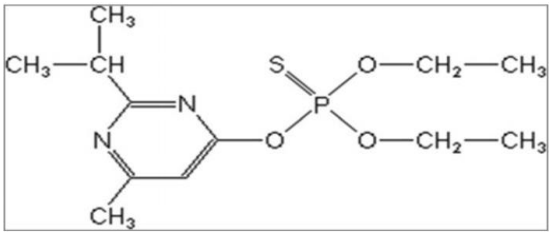

Fig 1: Chemical structure of diazinon [10]

The organophosphorus insecticide diazinon (Fig 1) is a colourless to dark brown liquid with a density of 1.116 g/cm², which is more than that of water. DZN has the Chemical Abstracts Service (CAS) registration number 333-41-5. The CAS name for diazinon is O, O-diethyl O-[6-methyl-2-(1-methylethyl)-4-pyrimidinyl] phosphorothioate.

b. DZN Uses

Diazinon is often used in veterinary medicine as a nematicide, acaricide, and insect repellant sprayed on poultry and animals [11-12]. DZN comes in a variety of forms, including dusts, granules, emulsions, oily solutions, microcapsules, ribbons, tags, aerosols, and seed dressings [13]. There are currently more than 500 diazinon-containing products available on the market, either alone or in combination with other pesticides [14].

c. Diazinon properties

The water solubility of DZN is rather high at 60 mg/L, and its boiling point is between 82 and 84 °C [14]. It takes 138 days to fully hydrolyse, whereas its half-life in soil was around 40 days. It is stable at pH 7 and does not easily volatilise from water and soil. Therefore, it can remain in the environment for up to six months [15]. DZN is oxidisable and decomposes at temperatures over 120 °C [16]. However, DZN degradation byproducts are harmful to both human and environmental health [17]. Furthermore, according to Begum *et al.* [18], DZN is classified as a nonsystemic (contact or surface) pesticide in nature.

DZN is one of the most frequently found OPs in groundwater, drinking water, and surface water, which is a particularly serious issue [19], as Pesticides with high water solubility may diffuse under the root area, sometimes contaminating groundwater, or get spread by surface drainage far from their use location [20].

d. DZN mode of action

Diazinon can affect a pest's body through contact, ingestion, or respiratory pathway [21]. The toxicity mechanism of DZN on insects is similar to that of other organophosphorus insecticides. Its mode of action relies on the phosphorylation of the amino acid serine in the active site of the acetylcholinesterase enzyme, which inhibits the cholinesterase enzyme [22]. AChE inhibition causes acetylcholine to build up at synapses between neurones, which prolongs the cholinergic receptors simulation. Consequently, the continous neurone stimulation causes intermediate symptoms such as anorexia, diarrhoea, generalised weakness, muscular tremors, altered posture and behaviour, depression, and insect mortality [23].

Despite the benefits of diazinon, it may be hazardous to non-target species [24]. Several investigations have shown residues of DZN in soil, water, and foods such as fruits, vegetables, and milk [25]. DZN converted into more hazardous degradate diazoxon by oxidative desulfurization, an activation process, after it has been ingested by both target and non-target species. Animals exposed to both the parent residue and the very poisonous oxon form as a result of the parent compound's metabolism to the oxon [22]. Diazoxon not only inhibits cholinesterase but also increases reactive oxygen species (ROS), leading to oxidative stress. Oxidative stress releases DNA and ruptures the mitochondrial membrane, causing cytotoxicity in different tissues [26].

e. DZN metabolism and toxicity

DZN is now being utilised in the Middle East in the veterinary and agricultural sectors, despite being prohibited in some countries [27]. The World Health Organisation classified it as a class II pollutant that is moderately dangerous [27-28]. It is important to emphasise that DZN has a closer link with insect AChE than with mammalian homologue enzymes. This fact results in significant variances in the LD50 dosage of DZN for mammals and insects [13]. Diazinon's toxicity to all animal species is dose-dependent; the larger the dose, the higher the mortality rate, coupled by a shorter mortality period [29].

DZN poisoning in animals happens as a result of contaminated food and water. After oral intake, DZN is quickly absorbed and dispersed throughout the body and undergoes extensive metabolism [30]. Cytochrome enzymes, also known as monooxygenase enzymes, such as CYP2C19, CYP1A2, CYP2B6, and CYP3A4, use oxidative desulfuration to convert DZN to diazoxon. These reactions occur mostly in the cells of the liver and intestines within the microsomal endoplasmic reticulum. Liver microsomes have a 5- to 10-fold greater DZN metabolism than enterocyte microsomes [13-14].

Liver is the primary organ involved in CYP metabolism and is in charge of the metabolism of pesticides that are ingested from the gastrointestinal system [31]. DZN and diazoxon may also be detoxified (deactivated) by microsomal enzymes like CYPs and esterases to produce the deactivated and non-toxic compounds 2-isopropyl-4-methyl-6-hydroxypyrimidine (IMHP), diethyl phosphate (DEP), and diethyl thiophosphate (DETP). Afterward, they were mostly eliminated in urine [30]. Accordingly, the toxicity resulting from diazinon exposures to non-target organisms will be determined by the equilibrium between activation and detoxification processes [32].

Since DZN is one of OPs, it exhibits the same general symptoms of OPs poisoning, which include emesis, stomach cramps, lacrimation, urine, faeces, and salivation. These symptoms are referred to as "SLUDGE" symptoms [33-34]. Furthermore, DZN's lipophilicity makes it easier for it to interact with the phospholipid bilayer of cell membranes of the majority of visceral organs [35]. As a result, DZN is harmful to several organs through the production of oxidative stress. According to several studies, it is a compound that is known to be cardiotoxic, immunotoxic, genotoxic, neurotoxic, hepatotoxic, cytotoxic, nephrotoxic, genotoxic, cytotoxic, cytotoxic, nephrotoxic, renal, and reproductive toxicity [36-42].

e.1 DZN-induced oxidative stress

A large number of diazinon's deleterious effects are produced by oxidative stress in addition to the suppression

of the acetylcholinesterase enzyme [43]. *In vitro* and *in vivo* studies have validated the significance of oxidative stress in the pathophysiology of DZN-induced tissue injuries [42]. Through the generation of reactive oxygen species, which in turn causes oxidative stress on glycolysis, mitochondrial respiratory tract, ATP production, amino acid metabolism, antioxidant defence system, and poison detoxification of the cell [44-45]. The incidence of oxidative stress following various DZN administration protocols has been examined in a number of studies. These protocols may include a single administration of increasing doses or after their prolonged administration (subacute, subchronic, or chronic) [46-49].

Previous findings reported that acute or subacute DZN poisoning causes lipid peroxidation (LPO) of cell membranes in the rat brain, heart, spleen, liver, and kidneys. This is characterised by a notable alteration in the activity of the antioxidant enzymes superoxide dismutase (SOD), catalase (CAT), and glutathione-S-transferase (GST), followed by alterations in lactate dehydrogenase (LDH) activity and malondialdehyde (MDA), and glutathione (GSH) levels [24, 25, 50, 51, 52]. Moreover, DZN causes oxidative damage to proteins with increases in the concentration of protein carbonyl groups and also increases Nitrite (NO2) concentrations [53-56].

DZN has been demonstrated to affect DNA integrity and induce cellular dysfunction by producing DNA adducts and lesions, single-strand and double-strand DNA breaks, and DNA and protein inter- and intra-crosslinks [57]. Furthermore, DZN exposure rises the frequency of micronuclei (genetic damage) produced by DNA strand breaks and oxidative stress-induced chromosomal abnormalities [58]. Studies by Naderi *et al*. and Ali *et al*. [59, 60] found that DZN intoxication promoted DNA fragmentation testicular spermatogenic tissue and hepatic tissues in mice. This degradation may be attributed to alkylating properties of organophosphorus chemicals.

e.2 DZN hepatotoxicity

The liver is essentially the first organ to experience severe oxidative stress from diazoxon because liver microsomal CYP450 enzymes convert DZN to diazoxon through oxidative desulphurization [61]. Given the liver's primary function in DZN metabolism and the correlation between DZN and oxidative stress, it can be concluded that oxidative stress plays a key role in DZN-induced liver damage [54].

Lipid peroxidation causes cell membrane disintegration, membrane fluidity reduction, membrane permeability enhancement, and cytoplasmic enzyme leakage [62]. The antioxidant system's depletion therefore causes hepatocellular death and necrosis, which is followed by a rise in the intracellular hepatic enzymes (ALT, AST, ALP, γ-GT, and LDH activities). The measurement of antioxidant levels for the evaluation of hepatocellular damage verified these increases. Additionally, histological techniques can reveal the extent of liver damage [63-64]. It was demonstrated that after diazinon administration, rats' livers exhibit periportal inflammation and necroinflammatory alterations [65]. Numerous publications have also shown hepatotoxicity and pathohistological alterations following acute [66], subacute [67-69], and subchronic exposure to diazinon in rats [70].

Previous research by Nassar *et al*. [58] found that oral treatment of DZN greatly elevated Bax, Caspase-3, Caspase-9, and the Bax/Bcl-2 ratio, whereas Bcl-2 dropped dramatically in liver and also protein carbonyl (PC) risen significantly followed by substantial declines in SOD, CAT, GST, and GPx levels. Fat change and hepatocyte necrosis can occur as a result of DZN's capability to impede protein synthesis and hydrolysis [71].

e.3 DZN nephrotoxicity

The kidney is a vital organ that performs a number of vital tasks, such as preserving homeostasis, controlling the extracellular environment, detoxifying the body, and getting rid of harmful substances and drugs. As a result, toxins may target the kidney [72]. DZN and its metabolites may be linked to kidney and renal tubule damage [73]. Rats given DZN showed large increases in MDA, H_2O_2, and NO in their renal tissue, which are indicators of oxidative and nitrosative stress, which is the imbalance between the production of reactive oxygen or nitrogen species and the antioxidant defence system. This imbalance promotes the generation of reactive oxygen species (ROS) and reactive nitrogen species (RNS) over the antioxidant defence system [74]. The RNS and ROS produced by DZN may impair the kidney's capacity to eliminate sodium, which results in sodium retention and hypertension. A decrease in the glomerular filtration rate (GFR) and an increase in salt retention impair the nephron's functional ability [74]. Additionally, as blood creatinine and urea nitrogen levels roughly correspond to the glomerular filtration rate, a rise in these parameters following DZN treatment indicated a severe deterioration in renal function [75 -76].

Renal histological alterations, including glomerular degeneration and kidney parenchymal shrinkage with leukocytic infiltration and congestion, were seen in many studies in experimental animals exposed to DZN. In addition, renal tubules had degenerative and necrotic alterations, including eosinophilic cytoplasm, broken cell borders, and blood capillary congestion between degenerated tubules [37, 67, 76]. Furthermore, histological analyses showed that the cortex was more damaged than the medulla. This may be partially caused by the unequal distribution of DZN and its metabolites in renal tissue, where the circulation carries approximately 90% of the entire renal blood flow to the cortex. Thus, the cortex may receive a higher bloodstream concentration of DZN and its metabolites than the medulla [74].

e.4 DZN reproductive toxicity

One of the primary targets of DZN toxicity is the reproductive system. DZN causes degenerative alterations in testicular tissue [77], a significant decrease in Leydig, spermatogonia, primary spermatocytes, and spermatid cells, poor sperm quality [78], and a decrease in serum testosterone levels that results in secondary infertility [79, 43]. Key cause of DZN reproductive toxicity is oxidative stress (OS) [80]. The DZN effect in the testis may target developing spermatozoa [81]. Through a variety of processes, it causes chromosomal damage, abnormalities, or the breakdown of sperm proteins, which eventually lowers sperm parameters [80]. DZN induced Sperm DNA fragmentation was previously reported by Salazar-Arredondo *et al*. [82] and Piña-Guzman *et al*. [81] as DZN exposure leads to nuclear protamine phosphorylation, which alters sperm chromatin condensation and DNA integrity.

Numerous experimental investigations have demonstrated that DZN can cause mitochondrial damage in sperm by reducing mitochondrial activity and causing the loss of mitochondrial membrane potential, affecting sperm motility, capacitation, and fertility rate [83-84]. This can be explained as

the proper function of sperm and the fertilisation process depend on mitochondria. They produce ROS and ATP, which are essential for healthy sperm activity and capacitation [85]. Additionally, they act as intracellular Ca2+ stores, and the membrane potential of these cells is essential for maintaining sperm motility and energy [86]. Histological study shows that animals intoxicated with DZN have minimal cytoplasmic carbohydrate accumulation in their spermatogenic cells. The shortage of energy sources may have caused the spermatogenesis cells to switch from using glucose to lipids [87].

Research conducted by Abou Hasan *et al.* [88] on rats to assess the toxicity of DZN on female rats' ovaries reported that a single dosage of DZN enhanced the amount of cells undergoing apoptosis and accelerated the atresia process in atretic follicles, Although the corpus luteum cells of the DZN-intoxicated rats showed multilamellar body forms and accumulations of big lipid droplets. DZN inhibited steroidogenesis in the rat ovary and STAR mRNA expression in cells affecting female fertility [89], as the transfer of lipids from the outer mitochondrial membrane to the inner membrane, a crucial step in the synthesis of steroid hormones, is regulated by the STAR protein, which also controls the luteinisation process of granulosa lutein and theca lutein cells [90].

e.5 DZN neurotoxicity

DZN was the first organophosphate to be recognised as a developmental neurotoxicant [91] Irreversible cholinesterase inhibition is the main target of DZN and its metabolites. DZN's suppression of AChE then causes ACh to build up at the connections between neurones, which raises the excitability of cholinergic receptors [92]. The neurotransmitter systems balance in cortical and subcortical areas is simply disrupted by excess ACh, which also modifies the ACh feedback loop [93-94]. According to Ahmed *et al.* [95], imbalances between provocative and suppressive neurones in various brain regions are another theory that might account for neurological consequences. Ultimately leading to muscarinic and nicotinic symptoms as well as indicators of intoxication in the central and peripheral nervous systems such as general weakness, anorexia, muscle convulsions, diarrhoea, abnormal behaviour, depression, and mortality after extended DZN exposure [14, 96]. Diazoxon is a more powerful AChE inhibitor in nerve tissues than its parent chemical, DZN (more than 1000 times) [96]. Prenatal DZN exposure can result in significant alterations in brain function. Studies identified deficits in glutamatergic [97], serotonergic, and cholinergic functions [98] in the brains of exposed kids. These neurochemical alterations are linked to numerous behavioural deficiencies, such as teenage hyperactivity and decreased risk-avoidance [99], poor passive avoidance learning [100], and changes in novel object recognition [97-99].

DZN exposure was reported to change expression of the hippocampus genes important for neurotransmission. It causes downregulation of the genes producing GABAB1 receptors, which are a key contender in the establishment of recognition memory [101]. Moreover, DZN exposure caused down regulation of the synaptophysin (SYP) gene, resulting in synaptic degeneration and substantial synapse loss in mice [102]. Also, Afshari *et al.* [103] found elevated TNF-α levels in the rat prefrontal cortex after 5 days of DZN administration.

e.6 DZN cardiotoxicity

Numerous investigations have revealed that cardiotoxicity is linked to DZN toxicity [104-105]. DZN caused left ventricular hypertrophy and decreased myocardial contractility, which led to heart failure [74]. It has been proposed that lipid peroxidation is one of the molecular processes behind DZN-induced cardiac damage [105]. Increases in the aminotransferases ALT and especially AST as well as alkaline phosphatase are indicators of cardiac injury, indicating that DZN damaged the pericardial membranes, allowing these enzymes to increase in the blood [74]. Additionally, it suggested that DZN may promote the generation of $O2\bullet^-$ by NADPH oxidase [106]. $O2\bullet^-$ and NO react to generate $ONOO^-$, which lowers NO's bioavailability and eventually results in hypertension. According to Ajibade *et al*, [74], NO is known to control cardiac contractility, restrict leukocyte adherence to the endothelium, influence vascular tone, and inhibit platelet activation.

e.7 DZN as endocrine disruptor

DZN is classified as an endocrine disruptor "having the potential to cause endocrine disruption." [77]. Pesticides with endocrine-disrupting activity alter an animal's endocrine system by interfering with receptor binding and disrupting hormone metabolism and steroidogenesis [107]. They have oestrogenic and antiandrogenic properties that can change the sex-steroid synthesis enzymes by acting on the hypothalamo hypophyseal-gonadal axis (HHG) [108]. This hormonal change modulates development and gonadal growth, which can lead to ovarian or testicular dysfunction [109]. DZN has been shown in recent studies to disrupt sex hormone levels, including testosterone and gonadotropin follicle-stimulating hormone (FSH), and luteinizing hormone (LH), which are the primary regulators of spermatogenesis and germ cell development [110].

e.8 DZN induced apoptosis and inflammation

Numerous cell types, such as ovarian follicular cells, sperm cells, cardiac muscle cells, peripheral blood lymphocytes, and skeletal muscles, have been shown to undergo DZN-induced cell death and apoptosis [83, 86, 111]. One of the primary ways that DZN causes apoptosis is thought to be through increased activity of caspases-3, -8, and -9, as well as increased Bax contents and decreased Bcl-2 (improved Bax/Bcl-2 ratio) [10]. Another important mechanism by which DZN promotes apoptosis is oxidative stress brought on by ROS [112]. Through the release of mitochondrial cytochrome c and the stimulation of caspases, the main initiators of apoptosis, ROS cause cell damage and death [113].

Pro-inflammatory cytokines such as IL-1β, IL-10, and TNF-α have been shown to rise in response to DZN [114-116]. This might be because DZN directly raises the mRNA expression of pro-inflammatory cytokines [117] or because the oxidative stress caused by DZN exposure triggered an inflammatory response [118].

e.9 DZN immunotoxicity

Exposure to diazinon has immunotoxic effects that are likely caused by changes in immune-related gene expression and modulation of the main cytokines [119]. Mice exposed to DZN have been shown to have histopathological alterations in the thymus and spleen as well as inhibition of humoral and cellular immune system function [120]. Additionally, phagocytic indices and splenocyte proliferation were significantly reduced in Nile tilapia exposed to DZN,

indicating immunotoxicity on both the innate and acquired immune responses [121-122].

In the great sturgeon fish, sub-lethal levels of DZN had an impact on innate immunological markers such as lysozyme and white blood cells. Additionally, Persian sturgeon fish exposed to sub-lethal dosages of DZN showed a reduction in lymphocytes and an increase in total neutrophils [123].

e.10 DZN induced hyperglycaemia

Prior research has documented hyperglycaemic and haemostatic alterations associated with glucose metabolism in DZN-exposed persons [40, 54]. The hyperglycemia impact of DZN is caused by two primary pathways. The first is the accelerated rate of gluconeogenesis, which produces glucose from non-carbohydrate sources by influencing glucose-6-phosphatase [G6Pase] and phosphoenolpyruvate carboxykinase [PEPCK]. Second, DZN-induced insulin resistance results from the decrease of insulin receptor expression and glucose transporter type 4 (GLUT4) because adipocytes secrete pro-inflammatory adipokines like TNF-α. This, in turn, causes a decrease in glucose uptake in adipose tissue [124].

AChE inhibition, a primary mechanism of DZN toxicity, can also increase the synthesis of adrenocorticotropic hormone (ACTH), which controls the production of cortisol.This hormone promotes gluconeogenesis and disrupts the action of insulin [125-127]. Animals exposed to DZN experience dose-dependent hyperglycemia. Blood glucose levels may also be impacted by an animal's gender; females are more likely to experience hyperglycemia after being exposed to DZN [128].

Conclusion

Diazinon (DZN) is an organophosphate insecticide frequently utilized to control insects, ticks, and mites. Its exposure may lead to OP toxicity in non-target organisms. OS induced by reactive oxygen species is the main mechanism associated with DZN toxicity. DZN has multi organ toxicity such as hematological and reproductive disorders, as well as kidney, liver, immuno-toxicity, and central nervous system toxicity. Understanding the harmful effects of DZN is critical for reducing their influence on animal health and directing future research efforts.

List of abbreviations

ACh	Acetyl Choline
AChE	Acetyl Choline Esterase
ACTH	Adrenocorticotropic hormone
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
Bax	BCL2 Associated X, Apoptosis Regulator
BCL2	Apoptosis Regulator
CAS	Chemical Abstracts Service
CAT	Catalase
CYP	Cytochromes P450
DEP	Diethyl phosphate
DETP	Diethyl thiophosphate
DZN	Diazinon
FSH	Follicle-stimulating hormone
G6Pase	Glucose-6-phosphatase
GFR	Glomerular filtration rate
GLUT4	Glucose transporter type 4
GPx	Glutathione peroxidase
GSH	Glutathione
GST	Glutathione s-transferase
H_2O_2	Hydrogen peroxide
HHG	Hypothalamo hypophyseal-gonadal axis
IL-10	Interleukin 10
IL-1β	Interleukin-1 beta
IMHP	2-isopropyl-4-methyl-6-hydroxypyrimidine
LDH	Lactate dehydrogenase
LH	Luteinizing hormone
LPO	Lipid peroxidation
MDA	Malondialdehyde
mRNA	Messenger ribonucleic acid
NADPH	Nicotinamide adenine dinucleotide phosphate
Nitrite	NO2
No	Nitrogen monoxide
O2-	Superoxide radical
ONOO–	Peroxynitrite
OPs	Organophosphate pesticides
OS	Oxidative stress
PC	protein carbonyl
PEPCK	Phosphoenolpyruvate carboxykinase
RNS	Reactive nitrogen species
ROS	Reactive oxygen species
SOD	Superoxide dismutase
STAR	Steroidogenic Acute Regulatory Protein
TNF-α	Tumor necrosis factor-alpha
γ-GT	Gamma-glutamyltransferase

Funding

No funding has been provided.

Conflict of Interest

The authors declare that they have no conflict of interest.

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