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Hepatoprotective Effect Of Infliximab Against Hepatotoxicdrugs (Paracetamol, Methotrexate And Carbon Tetrachloride)

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Abstract: Liver is a versatile organ which performs multiple functions.The gastrointestinal homeostasis and body function in general is maintained by the liver.The liver injury occurs when the parent compound is metabolized into highly active metabolites which combinewith the macromolecules that include proteins, lipidsand nucleic acids with the resultant loss of cellular integrity and dysfunction.Consequently, it is not surprising that liver diseases are the major cause for morbidity and mortality.Tumor Necrosis Factor (TNF)is the vital mediator ofpatho- physiological conditions leading to hepatocellular damage and activation of HSC and extracellular matrix deposition the hallmarks of liver fibrosis, TNF not only is an inducer of hepatocellular damage, but also as a pro-fibrogenic factor in the liver. Hepatotoxic drugs target the liver cells, alter the metabolic pathway and hinder normal function by causing destruction or degeneration of hepatic cells. Hepatotoxic drugs mainly activate TNF. The toxicity induced by Paracetamol, Methotrexate and Carbon tetrachloride, the resultant hepatocellular damage envisaged by these drugs and the role anti -TNF antibody infliximab as a hepatoprotective drug is illustrated in the present review.

Keywords: Hepatotoxicity, Paracetamol, Methotrexate, Carbon Tetrachloride,Tnfα, Infliximab

1. INTRODUCTION

Liver, the largest organ of the body, present below the diaphragm on the upper right quadrant of the abdomenis four lobed wedge- shaped, reddish-brown coloration and weighs about 1.5 Kg. Liver is a versatile organ which performs multiple functions. It is an important organ for metabolism and elimination of drugs. Subsequently, it is not surprising that liver diseases are the major cause for morbidity and mortality. The gastrointestinal homeostasis and body function in general is maintained by the liver. Approximately,75% of blood supply in the liver is from the gastrointestinal organ and spleen through portal veins hence the drugs and xenobiotics are in concentrated forms. Thus, the liver injury occurs when the biotransformation of the parent compound results in highly reactive metabolites that combines cellular macromolecules like proteins, lipids, nucleic acids to cause cellular disintegrity and dysfunction [1,84]. Consequently, the liver is prone to many diseases which are referred to as hepatic disease. The liver diseases are characterized by viral infection (hepatitis), cancer or tumor, autoimmune disease, cirrhosis, fibrosis, necrosis, acute cholestasis, micro vesicular steatosis[2]

2. Liver Injury

There are numerous factors that contribute to liver injury [3].Drug induced liver injury is theprimesource for both acute and chronichepatotoxicity[4]. Approximately, 1000 drugs are known to cause liver diseases. However, the chances of liver injury depend on the chemical properties of drugs, genetic and environmental factors. The etiology of drug-induced liver injury is due to the toxic drugs or their metabolites which modifies immune response or directly alters the biochemistry of the cell leading to cell-death[5,6]

Tumor Necrosis Factor (TNF-α) and liver injury

TNF (Tumor Necrosis Factor) is an important mediator to patho- physiological conditions leading to hepatocellular damage that accelerates the Hepatic Stellate Cell (HSC) and facilitates the deposition of extracellular matrix, the hallmarks of liver fibrosis. TNF not only is an inducer of hepatocellular damage, but also as a pro-fibrogenic factor in the liver[7] TNF-α is a vital protein synthesized in our body as an immune reaction to infection. However excess production of TNF -α can lead to destruction of cartilage, bone and various tissues involved in metabolic pathways. Infliximab,also known by the trade name Remicade blocks the action of TNF-α, which in turn suppresses the immune system thereby reducing inflammation and the related symptoms [8,43] Hepatotoxic drugs mainly activateTNF (figure.1). The interaction between soluble (s- TNF) with TNFR1 and membrane (m-TNF) with TNFR2 results in activation of IKK and JNK pathways by the adapter molecules TRADD, TRAF2, and RIP. The excessive stimulation of the downstream signaling molecule JNK acceleratesinflammatory responses and apoptosis which then results in destruction of hepatocytes[9]. The reactive oxygen species (ROS) production is essentialfor activation of JNK that in turn is involved in oxidation and inactivation of variousMAP kinase phosphates (MKPs). Actually, JNK activation induces phosphorylation of E3 ligase itch, ubiquitination and deprivationof NFBdependent Caspase 8 inhibitor c-Flip.Furthermore, activation of Nf-B blocks the prolonged stimulation of JNK and prevents the cell death through antioxidant production (MnSOD) [10,11]

3. Hepatotoxic Drugs

3.1 Paracetamol (Acetaminophen)

Paracetamol (N-acetyl –p-aminophenol) also known as acetaminophen is widely used as analgesics and antipyretic agents. Initially, paracetamol did not cause methemoglobinemia, hence, therapeutic use of paracetamol reached greater heights. In 1950's, the drug was available globally as an antipyretic and analgesic drug and one of themost frequently used over the counter drugs in several countries. Contrastingly, overdose of paracetamol leads to fulminant hepatic failure. Paracetamol is

mainly hepatotoxic, with the characteristic symptoms centrilobular hepatic necrosis with nuclear pyknosis and eosinophilic cytoplasm that extends toenlarged hepatic lesions. The factors that contribute to hepatotoxicity in experimental animals are age, sex and variation of interspecies [12,81]. Furthermore, rationale of combining a highly addictive drug (opiate) with paracetamol resulted a dose-dependent hepatotoxicity [13,81] The hepatotoxicity caused is not by paracetamol itself but due to the formation of intermediate metabolites during the metabolism. Paracetamol is detoxified via glucuronidation and sulfation in the liver. The reactive metabolite which is electrophilic in nature is conjugated with hepatic glutathione (GSH) and eliminated mainly as mercapturic acid in urine[14] On over dosage of paracetamol, glucuronidation and sulfation routes become saturated and within 1-2 hours there is a massive depletion in the hepatic GSH level.Thus, covalent interaction between the metabolite, N-acetyl-P-benzoquinoneimine with theintracellular macromolecules induces hepatocellular damage and necrosis[15.16] Acetaminophen/paracetamol induced liver injury mainly in hepatocytes, which play a key role in metabolism.The cytochrome p450 enzyme system is responsible for the metabolism of paracetamol to form N-acetyl-p-benzoquinone imine (NAPQI).However, when hepatic GSH is depleted, excessive NAPQI binds to cellular proteins covalently, and brings about mitochondrial dysfunction, oxidative stress, and ATP depletion.The oxidative stress in turn leads to the nitration of mitochondrial proteins, the DNA damage of mitochondrial, ultimately resulting in the mitochondrial permeability transition and cell death [17.18]

3.2 Methotrexate

Methotrexate is a folic acid antagonist, extensively used in lymphoma,leukemia, and several solid organ tumors[19].Methotrexate is a powerful immunosuppressant usedin the treatment of autoimmune diseases.Methotrexate (aminopterin derivative) was developed in late 1940's. The rapidly multiplying cells are more susceptible to cytotoxic effects of methotrexate as methotrexate acts actively on the dividing cells in S- phase [20]. Previously, methotrexate was approved in chemotherapy of cancer in the United States(1955), psoriasis (1972) and rheumatoid arthritis (1988) andpreferred for all these conditions until today [21]. The folate antagonist acts by inhibiting the dihydrofolate reductase enzyme (DHFR), which results in limited or no conversion of folic acid to tetrahydro folic acid.Tetrahydrofolate maintains the intracellular pool for the purine nucleotide and is also involved in thymidylate synthesis. The action of methotrexate not only impairs the proliferating malignant cells but also impairs the normal proliferating cells in bone marrow cells, fetus, buccal and intestinal mucosa and urinary bladder[22]. The blockade of DHFR results in reduction of nucleic acid synthesis due to impaired thymidylate and purine biosynthesis,mainly DNA synthesis, repair and replication [23]. Methotrexate augments serum aminotransferase activity and prolonged therapy has been linked to fibrosis, fatty liver disease and cirrhosis[25]. The mechanism of liver injury is due to direct toxicity that involves blockade of nucleic acid synthesis(RNA and DNA) in the liver and arrests the cellular multiplication that end in the steatosis and hepatic fibrosis[26]

3.3 Carbon Tetrachloride

Carbon tetrachloride (CCl_4), obtained from reaction between chloroform and chlorineis household cleaner, degreaser and an industrial solvent. The use of CCl_4 gradually decreased due to its toxicities. Nowadays CCl4 are extensively used as a model drug to study the hepatotoxic effects.[27].CCl_4 is activated by the liver enzymes mainly by cytochrome to form a highly reactive radical, trichloromethylradical (CCl_3). CCl_3 radicals bring about impairment of cellular processesinlipid metabolism that leads to steotosis. CCl_3 on oxidation is converted into a more highly reactive free radical trichloromethylperoxy radical (CCl_3 OO). The free radical CCl3 OO initiates lipid peroxidation that induces disruption of phospholipid bilayer thereby affects the permeability of mitochondria, endoplasmic reticulum, loss of homeostasisresultant cell damage [28]. The activation of, nitric oxide,tumor necrosis factor and transforming growth factors alpha and beta in the cell by CCl4 and alteration of cellularprocesses causesself-destruction or fibrosis at the molecular level [29,30,31]

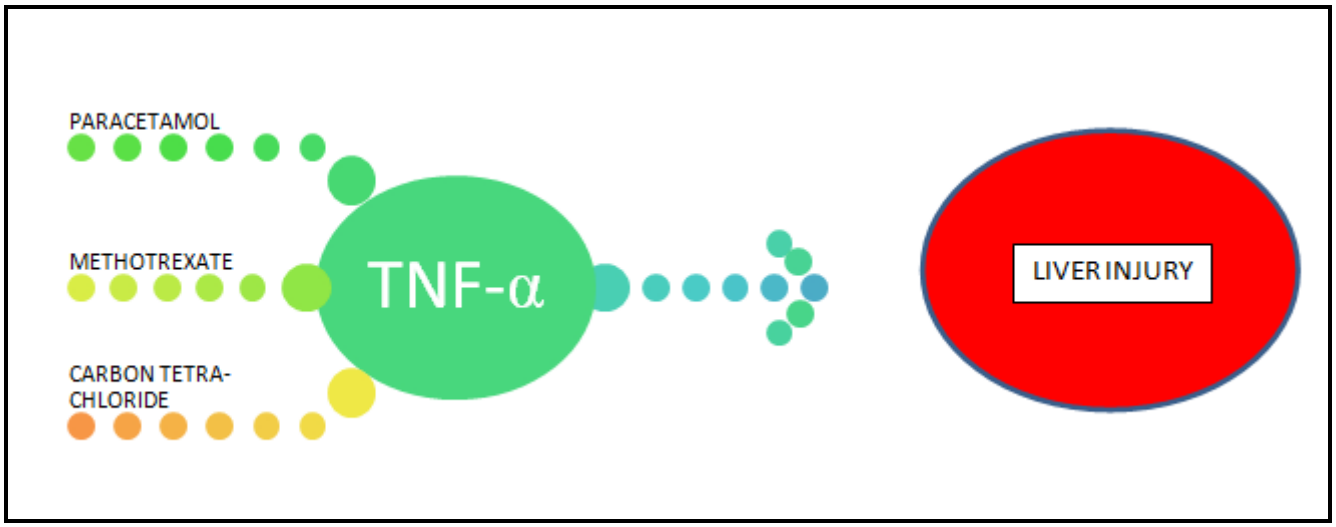

Figure 1. Hepatotoxic drugs and liver injury

4. Infliximab to counteract hepatotoxicity

Infliximab first approved drug (U.S. Food and Drug Administration (FDA)(1998))and European Medicine Agency (EMA)(1999), Pharmaceuticals and Medicals Devices isused as Reference medicine in pharmacotherapy of Behcet's disease, ankylosing spondylitis,inflammatory bowel disease,Crohn's disease, atopic dermatitis, Rhematoid arthritis and Psoriatic arthritis as orphan drugs. The monoclonal antibody of TNF alpha possesses potent anti-inflammatory effect and reduces the structural damage, induces remission and minimizes the usage of steroids, hospitalization and surgeries in serious inflammatory conditions [32-37] This monoclonal antibody was developed using recombinant DNA technology by combining the IgG of mouse and human. Hence it is called as chimeric monoclonal antibody. This drug is administered for treating a variety of autoimmune disease. Infliximab acts by preventing thebinding offree floating soluble and transmembrane forms of TNF-α with receptorsand neutralizes most of the biochemical actions of TNF-α[38,39] Some of the adverse effects are serious infection, reactivation of hepatitis B, acute hepatic injury, psoriasis, demyelinating central nervous system disorder, vitiligo, hepatosplenic T-cell lymphoma [40]. Hepatotoxicity is associated with elevation in serum aminotransferase, hepatocellular injury, cholestasis, reactivation of hepatitis B [41].

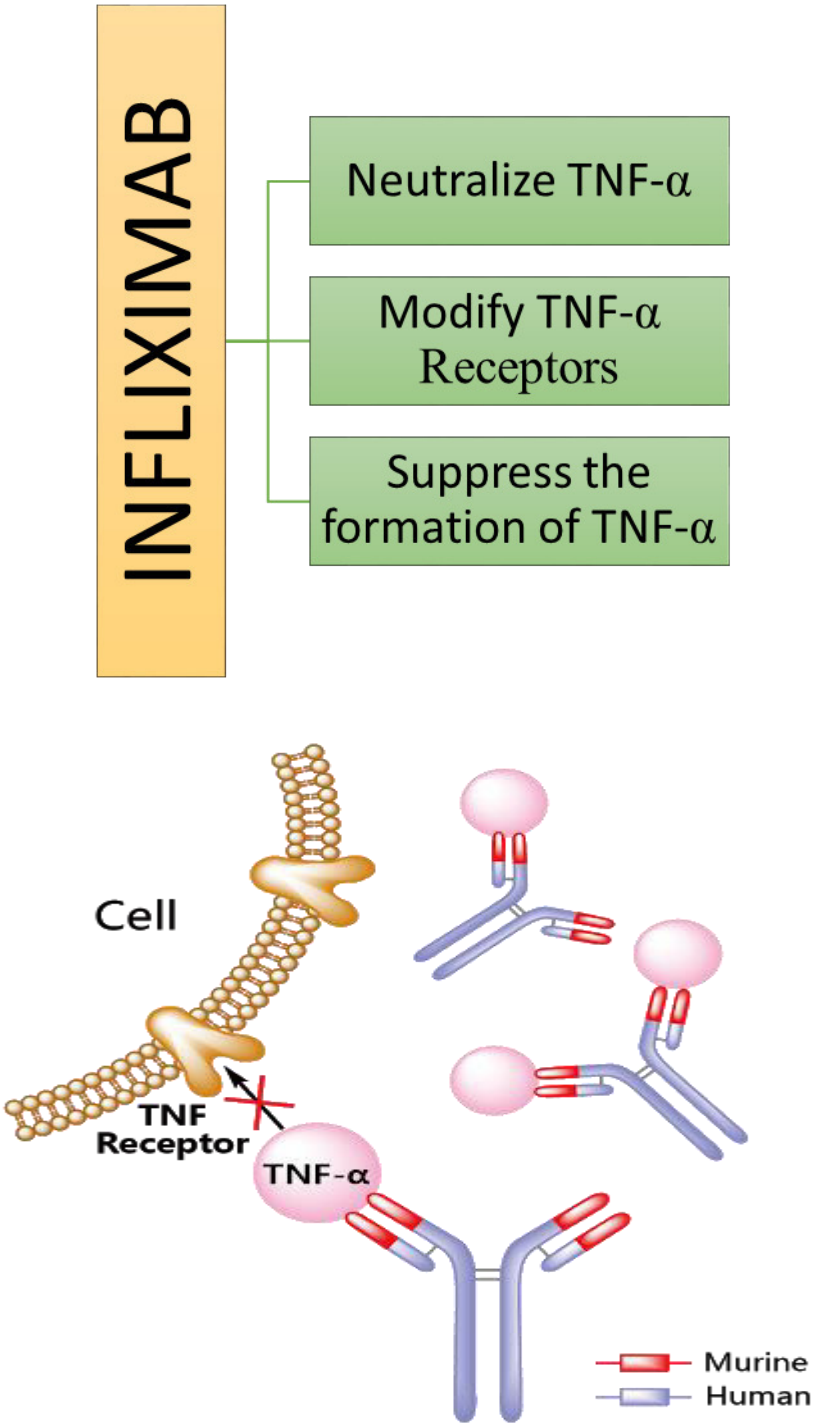

Figure 2. Infliximab and mechanism of TNF inhibition

4.1 Possible Mechanism of Protective Activity of Infliximab

Infliximab acts by blocking TNF-αbinding to its receptor and inhibiting transmembrane proteins. The TNF-α activates the cytokines induced inflammatory responses that includes release of interleukin-1 (IL-1) and IL-6,migration of leukocyte; eosinophil and neutrophil and stimulation of tissue degrading enzymes and acute phase reactants [42,43]. The functional activities of TNF-α can be neutralized with the treatment of infliximab which shows an overall reduction in the inflammation. Infliximab therapy results in the reduction of IL -1 and IL - 6 production, leukocyte migration and expression of adhesion molecules by leukocyte and endothelial cells. The drug also causes limitations of the biological activities of eosinophils and neutrophils and decreases the generation of degrading enzymes made by chondrocytes and synoviocytes. The anti-TNF-α-mediated mechanisms of liver damage include (A) blockade of TNF-α thatcausesimpairment or suppression of auto-reactive B cell synthesis and enhancement of lymphocyte due to apoptosis of CD8 T cells and triggers the autoantibodies development; (B) a dual antagonizing effect exerted by TNF-α on two TNF receptors ie(TNFR1 and TNFR2) expressed on T cells that can lead to inflammatory response.TNF-α Binds mainly to TNFR1and stimulates the effector T cell, initiating inflammatory response.WhereasTNF-α Binds to TNFR2, expressed on the regulatory T cells, result in the attenuation of inflammation and also prevent autoimmunity [45]. The response may be influenced by immunological and genetic variation in individual [46-48]
Infliximab, an anti-TNF-α agent, possibly shows the protective activity by binding to TNF-α and neutralizing them. Thus, the release of TNF-α as a result of hepatotoxicity by the intake of hepatotoxic drugs such as paracetamol, methotrexate, carbon tetra-chloride can be attenuated by the infliximab(figure.2) [49,50].
Activation of Tumor necrosis factor-α (TNF-α) a prototype of the TNF family secreted by macrophages is the main cause for hepatic injury and inflammation [51,52]. TNF-α attaches to its receptors (TNF-R1, TNF-R2) and stimulatesseries of intracellular cascades and activates NF-κB which in turn provokes cellular activation, differentiation, cytokine production and apoptosis [53]. Additionally, exert pro-apoptotic effects on T cells and block the production of Th1 type of cytokines. The TNF-α is blocked by infliximab, suppressing the proinflammatory cytokine release and regulation of the purine metabolism [54,55]. Toxicity of infliximab may be transient ischemia to serious anaphylactic reactions that includes upper respiratory tract infection (32%),misc. Antinuclear antibodies (~50%) Infection (36%), GI -Nausea (21%),complement activation, (20%; severe <5%),abdominal pain (12%; Crohn's 26%) and Infusion reactions which includes cytokine release syndrome(cytokine storm, IgG mediated Type -1 hypersensitive and anaphylacticdegranulation of mast cell'sreaction [56-59].

4.2 Evaluation of protective activity of Infliximab

4.2.1Paracetamol (Acetaminophen)

The increase in serum enzyme levels is the biomarker of liver injury. Generally, thevaluesof AST and ALT areused aspreclinical and clinical markers for the prediction of liver injury. These enzymes located in cytosol are released into the circulation when the liver cells are damaged. Hence, they are considered as essential markers to evaluate the extent of hepatocellular injury In a study, acetaminopheninduced hepatotoxicity in rats, the level of AST and ALT in the serum reached high levels indicating high level of hepatocellular damage. But the levels of serum enzymes became normal on administration of infliximab (Table 1). This shows the attenuation of liver cell injury by the infliximab and thus the cytosolic release of serum enzymes is controlled[60-63].

TABLE 1: Serum AST and ALT levels of Paracetamol and Infliximab (Irmak Ferah,et.al, 2013)

Serum level	Control	Infliximab	Paracetamol	Paracetamol+infliximab
ALT (U/L)	43.38 ± 10.18	40.13 ± 2.37	175.13 ± 63.63	50.05 ± 6.46
AST (U/L)	77.06 ±12.11	73.00 ± 10.51	221.38 ± 68.58	94.25 ± 26.12
TNF-α (pg/ml)	35.25 ± 10.38	30.50 ± 7.84	181.00 ± 40.96	47.50 ± 6.80

Paracetamol toxicity also enhances oxidative stress and lipid peroxidation which gradually leads to cell damage. Oxidative stress leads to accumulation of free radicals and peroxidation of lipids leads to malondialdehyde (MDA) production, the end product of lipid peroxidation. According to previous researchers, high dosage of paracetamol intake increased accumulation of MDA in the liver tissue. Subsequently, on treatment with infliximab, declineof MDA levels was observed in the liver tissue. Hence, the evidence suggests that treatment of paracetamol induced hepatotoxicity with infliximab shows beneficial effects[64-65].

4.2.2 Methotrexate

The earlier in-vivo study indicates thatoverdose of methotrexate administrationcauses rapid increase in serum AST and ALT levels due toliver cell damage. However, on treatment with infliximab the level of the serum enzymes were normalized (Table 2) [24].

TABLE 2: Serum AST and ALT levels of Methotrexate and Infliximab (Cure, et.al, 2015)

Serum level	Control	Infliximab	Methotrexate	Methotrexate+Infliximab
ALT (U/L)	35.1 ± 6.6	35.9 ± 5.8	46.2 ± 13.6	44.0 ± 13.8
AST (U/L)	34.0 ± 7.7	33.7 ± 4.2	66.4 ± 10.2	53.6 ± 16.8
TNF-α (pg/ml)	310.2 ± 54.9	285.1 ± 39.6	449.1 ± 95.1	360.9 ± 53.7

Methotrexate induced toxicity also showed an increased oxidative stress. As a result the proinflammatory cytokines are released into the circulation thus enhancing the liver cell damage. But on treatment with infliximab, TNF-α inhibitory agent,

shows excessive suppression of proinflammatory cytokines and protective against the liver injury[66-69] Additionally, Infliximab reduces the cellular defense mechanism against tumor cells due to alteration in arginine level, an essential mediator that influences immune responses [70,82]

4.2.3 Carbon Tetrachloride

CCl_4 is used as a reference drug for inducing liver toxicity in experimental models. Hence,the increase in hepatocellular damage is evaluated by clinical markers such as serum enzyme levels, lipid peroxidation, oxidative stress, fibrosis. In a study, administration of CCl_4 showed rise in the serum AST and ALT levels. TNF-α is involved in pathogenesis of liver fibrosis due to the activation of the Kupffer) and involved in cell differentiation, stimulation, immunomodulation, and proinflammatory activity.On further treatment with infliximab, TNF-α inhibitory agent, showed reduction in the serum enzyme levels. It may possibly be due to the suppression of TNF-α activity andthereby apoptosis by infliximab(Table 3)[71-73] Furthermore, infliximab reduces the fibrogenic and necro-inflammatory activity of CCl4and prevents hepatic fibrosis due to CCL4. In addition, infliximab causes blockadeof the IL-6 release from Kupffer cells that in turn may modify cytokine and enhances anti-fibrotic effect [74-76,83]

TABLE 3: Serum AST and ALT levels of CCl_4 and Infliximab (Table 3) (Sehitoglu, et.al, 2015)

Serum level	Control	CCl_4	CCl_4 + Infliximab
ALT (U/L)	60.1 ± 19.9	917.6 ± 142.9	540.8 ± 313.4
AST (U/L)	197.5 ± 21.0	1375.3 ± 282.6	962.2 ± 535.1
TNF-α (pg/ml)	74.9 ± 18.4	134.3 ± 35.3	111.6 ± 8.7

The oxidative stress induces the production of reactive oxygen species (ROS) and peroxynitrite. The accumulation of ROS exacerbates the liver injury and leads to dysfunction of the hepatic cells. On administration of infliximab, TNF-α inhibitory agent, the ROS levels reduces thereby prevents the cellular damage [[77-80,85]

5. CONCLUSION

The concentration of TNFα is vital for determining the fate of the cell. Previous studies suggest the elevated concentrations of TNF-α enhanced the processes of cell death in hepatocytes, but minimum concentrations of TNF-α facilitates the survival of the liver cells.The present study concludes that Infliximab can counteract the hepatotoxic effects produced by the hepatotoxic drugs that include paracetamol,methotrexate and CCl4, by minimizing ROS productionthrough the inhibition of TNF-α.

CONFLICT OF INTEREST

Conflict of interest declare none.

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