



# Metformin Ameliorated Valproic Acid Induced Hepatotoxicity in Male Rats

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## Abstract

Valproic acid is commonly used to treat a variety of psychiatric disorders, including epilepsy, bipolar disorder, and migraine headaches. It has been shown that its use may result in adverse consequences such as hepatotoxicity. This study investigated the potential hepatoprotective effect of metformin against valproic acid-induced hepatotoxicity in male rats. Metformin (125, 250, and 500 mg/kg/day) was received for 30 days, and valproic acid (400 mg/kg/day) was received starting from the 22nd day of the experiment for eight days to induce hepatocellular damage in rats. Valproic acid showed elevated serum liver enzymes and decreased total antioxidant capacity (TAC). At the same time, valproic acid treatment increased tumor necrosis factor alpha (TNF- $\alpha$ ) production and nuclear factor Kappa B (NF- $\kappa$ B) expression. These results were supported by histopathological evaluation.

**Key Words:** Metformin, Valproic Acid, Liver Enzymes, TAC, TNF- $\alpha$ , NF- $\kappa$ B.

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## Introduction

Valproic acid (V.A), or valproate, is a commonly used antiepileptic drug to treat epilepsy, bipolar disorders, and migraines. Despite its medical effectiveness, significant problems such as hepatotoxicity have been recorded following V.A use<sup>(1)</sup>. Many metabolites were formed during V.A metabolism via the liver, which may relate to hepatotoxicity<sup>(2)</sup>. The main causes of hepatotoxicity by V.A were oxidative stress due to excessive production of reactive oxygen species (ROS) and unbalanced antioxidant efficacy due to alteration of lipids, proteins, and nucleic acids<sup>(3)</sup>. In addition, histological results in the liver found sinusoidal dilation and congestion, inflammation, swollen hepatocytes, and necrosis<sup>(4)</sup>. Furthermore, it has been shown that V.A-induced liver injury is associated with inflammatory reactions as shown by increased levels of inflammatory mediators such as tumor necrosis factor-alpha (TNF- $\alpha$ ), and nuclear factor kappa B (NF- $\kappa$ B)<sup>(5)</sup>. Mechanisms for promoting redox homeostasis should be maintained to balance the excessive generation of free radicals over oxidative stress. Metformin has been extensively explored for its efficient

antioxidant<sup>(6)</sup>, <sup>(7)</sup> and anti-inflammatory abilities in sustaining cell function<sup>(8)</sup>. Metformin activated AMPK in hepatocytes by blocking complex I and altering the ATP/AMP balance<sup>(9)</sup>. Activated AMPK can also suppress a variety of inflammatory processes, including mTOR-related TNF- $\alpha$  and NF- $\kappa$ B activation<sup>(10)</sup>, and it has antioxidant properties due to its inhibition of the NAD(P)H/PKC oxidase pathways<sup>(9)</sup>.

## Materials and Methods

### 1. Animals

Forty-eight adult male albino rats; weighing 150 - 220 gm, were used in this study. They were purchased and placed in the animal house of the College of Pharmacy/ Mustansiriyah University. Animals were housed under controlled environmental conditions ( $23 \pm 1^{\circ}\text{C}$ ), and light 12/12 hours light/dark cycle). They were given pellets and water freely. The investigation was approved by the Ethics Committee of the College of pharmacy/ Mustansiriyah University.

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## 2. Drugs and Chemicals

Valproic acid as sodium salt (V.A) obtained from Sigma-Aldrich (St Louis, MO, USA), metformin purchased from (Pioneer Pharmaceutical Company). V.A and metformin were prepared in distilled water (PDPL; India).

## 3. Experimental Design

Forty-eight rats were randomly placed into eight groups (6 per each). Group I (Control): animals received distilled water. Group II, III, and IV: rats received metformin (125, 250, and 500 mg/kg/day respectively, orally for 30 days. Group V (V.A): rats were injected with V.A (400 mg/kg/day; i.p) for 8 days to induce hepatotoxicity; beginning on the 22th day of the experiment. Groups VI, VIII, and VIII: rats receiving metformin orally via gavage at doses of 125, 250, and 500 mg/kg/day separately for 30 days and V.A (400 mg/kg; i.p) beginning on 22nd day of the experiment for 8 days. One day following the last therapy, rats were anesthetized intraperitoneally with 50 mg/kg ketamine and 5 mg/kg xylazine. Blood samples were obtained from the right ventricle of the heart and centrifuged for 15 minutes at 2500 rpm to obtain serum for oxidative parameter estimation. Following euthanasia, liver tissues were promptly dissected and washed from adherent tissues with ice-cold saline. Parts of each group's livers were preserved in 10% formalin saline for histological estimation. Tissues from the same part of the liver were obtained from all groups and homogenized in phosphate buffer to estimate inflammatory markers.

## Biochemical Analysis

### 1. Assessment of Oxidative Stress

The status of oxidative stress was evaluated by estimation of total antioxidant capacity (TAC) levels in the serum by using rat total antioxidant capacity (TAC) competitive ELISA kit (MyBioSource; MBS733414\_48T) according to the manufacture guide. The serum sample and buffer are incubated with TAC-Horseradish Peroxidase conjugated in a pre-coated plate, and following a washing step to remove unbound antibodies, incubated with HRP enzyme substrate to generate an enzyme-substrate reaction, and blue color develops. The stop solution was used to stop the reaction that produces the yellow color. Color intensity was measured at 450 nm.

### 2. Assessment of Inflammatory Factors

Inflammation was assessed by estimation TNF- $\alpha$  and NF $\kappa$ B contents in liver homogenates by using sandwich ELISA kits (MyBioSource; MBS2507393, MBS268833) respectively, according to manufacturer procedures). The ELISA plate has been pre-coated with anti- TNF- $\alpha$  or NF $\kappa$ B antibodies specific to rats. A sample and a standard were added and incubated to enable bonding specific antigens to capture antibodies placed on the wells. After that, the wells were washed to eliminate unbound antigen. The biotinylated detection anti- TNF- $\alpha$  or NF $\kappa$ B antibodies and the conjugate, Avidin-Horseradish Peroxidase (HRP), were placed in each well and incubated. Unbound components were washed. The substrate was then put into each well, and the blue color developed. The stop solution was added to terminate the enzyme-substrate reaction, and the yellow color was formed. Color intensity can be measured at 450 nm.

### 3. Histopathological Examination

After 24 hours of fixing liver tissues in 10% formalin saline, the samples were processed for paraffin embedding to create 4 mm slices thick. The samples were stained with hematoxylin and eosin (H&E) and examined under a light microscope. The severity of the detected histopathological damage was assessed as follows: (0) normal hepatocellular lobules structure (+) mild hepatocellular lobules damage (++) moderate hepatocellular lobules damaged, and (+++) severe.

### 4. Statistical Analysis

The data were presented as means + SEM. One-way analysis of variance (ANOVA), followed by the Tukey test, was used for results analysis. For all statistical tests, the results are considered nonsignificant if they are  $P$ -value > 0.05 and significant if they are  $P$ -value < 0.05.

## Results

### 1. Antioxidative Effect of Metformin on V.A- Induced Hepatotoxicity in Rats

TAC was measured in the serum after V.A administration and treatment with 125, 250, and 500 mg/kg/day dosages of metformin. The results showed that TAC levels in the groups receiving metformin without V.A had a nonsignificant

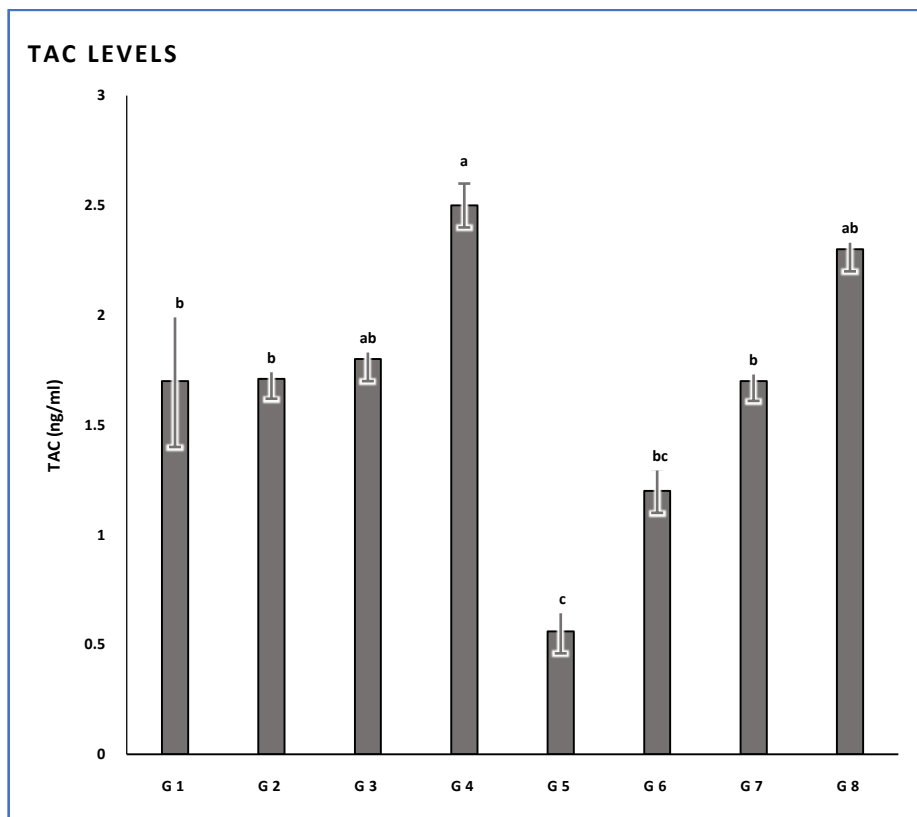


difference with the control group (p-value > 0.05). The TAC level in group I is slightly lower than in groups II, III, and IV. This level is highest in the last three groups, especially in group IV, which consumed the maximum dose of metformin. In group V (V.A), the TAC level significantly decreased (p-value<0.05) when compared to group I (control). In groups VI, VII, and VIII, consumption of metformin (at increasing dose) plus V.A has been shown to increase the TAC level and approximately return to normal when compared to control and metformin groups, respectively (p-value >0.005) but group VI remained non significantly different (p-value > 0.005) when compared to group V. Low TAC levels were corrected by an increased dose of metformin, especially in group VIII. As a result, the greatest and lowest TAC levels are connected to groups IV and V, respectively. It appears that increasing the metformin dosage can raise the TAC level, as shown in table 1 and Figure 1.

**Table 1.**Effect of metformin on TAC levels in all groups

Groups	TAO (ng/ml)
G1	1.7 ± 0.3 <i>b</i>
G2	1.71 ± 0.09 <i>b</i>
G3	1.8 ± 0.1 <i>ab</i>
G4	2.5 ± 0.1 <i>a</i>
G5	0.56 ± 0.1 <i>c</i>
G6	1.2 ± 0.1 <i>bc</i>
G7	1.7 ± 0.09 <i>b</i>
G8	2.3 ± 0.1 <i>ab</i>

Each value is given as the mean ± SEM. The statistical analysis was done by using one-way ANOVA followed by the Tukey test. G1: negative control group, G2:125mg/kg metformin group: G3: 250mg/kg metformin group, G4:500mg/kg metformin group, G5: positive control group (400mg/kg V.A), G6: 125mg/kg metformin + V.A, G7: 250mg/kg metformin + V.A, G8: 500mg/kg metformin + V.A. Different lower - case letters indicate a significant difference among groups.



**Figure 1.**Change total antioxidants (TAC) levels in all groups

The results represented as mean ± SEM. The statistical analysis was done by using one-way ANOVA followed by the Tukey test. G1: negative control group, G2:125mg/kg metformin group: G3: 250mg/kg metformin group, G4:500mg/kg

metformin group, G5: positive control group (400mg/kg V.A), G6: 125mg/kg metformin + V.A, G7: 250mg/kg metformin + V.A, G8: 500mg/kg metformin + V.A. Different lower - case letters indicate a significant difference among groups.



**2. Anti-inflammatory Effect of Metformin on V.A – Induced Hepatotoxicity Rats**

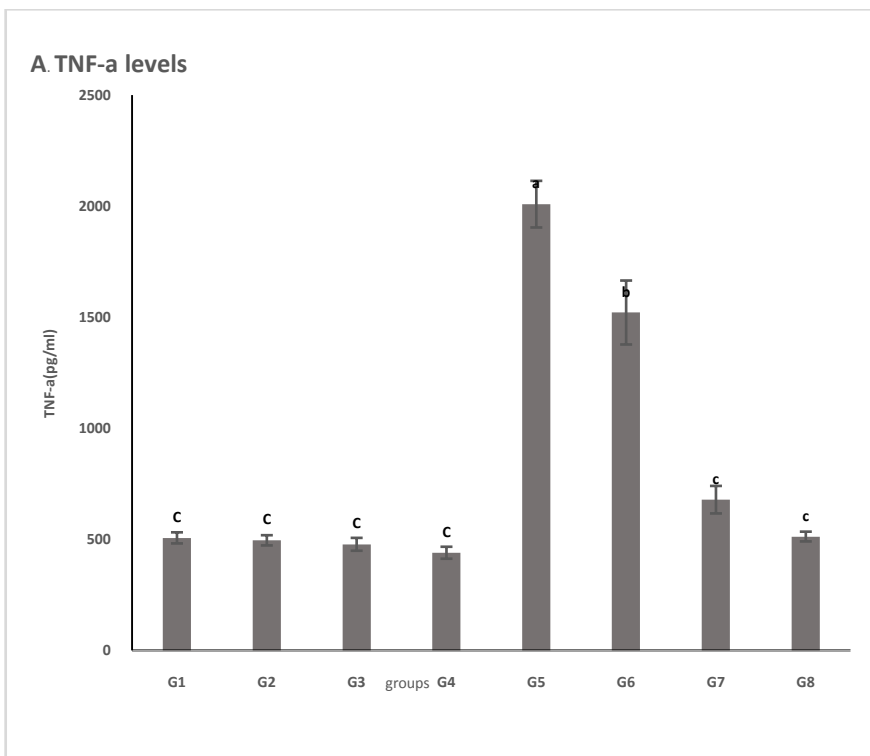
Groups receiving metformin without V.A have been nonsignificant difference in levels of TNF-  $\alpha$ , and NF- $\kappa$ B when compared with control group (p-value > 0.05). TNF-  $\alpha$  level in the group I is slightly higher than in groups II, III, and IV. This level is lowest in the last three groups, especially in group IV which has lowest value for TNF-  $\alpha$ , and NF- $\kappa$ B. Group V (V.A alone) revealed a significantly increased (p - value < 0.05) in TNF-  $\alpha$  level (2009  $\pm$ 105pg/ml), and NF- $\kappa$ B levels (3.5  $\pm$  0.1 ng/ml) as compared to group I, II, III, and IV. In group VI, showed a significantly decreased TNF- $\alpha$  and NF $\kappa$ B levels (*P-value*< 0.05) when compared to G5, but TNF-  $\alpha$  remained significant differences when compared to group I and group II (*P-value*< 0.05). in contrast NF $\kappa$ Bwas significant differences when matched to group I (p-value < 0.05) and non-significant when matched to group II (p-value > 0.05). In group VII, and VIII, consumption of metformin (at increasing dose) plus V.A showed significantly decreased the levels of TNF- $\alpha$  and NF $\kappa$ B and approximately return to normal when compared to control and metformin groups respectively (p-value > 0.005). low levels of TNF- $\alpha$  and NF $\kappa$ B were corrected by

increased dose of metformin, particularly in group VIII. as shown in table 2 and Figure 2.

**Table 2.** TNF- $\alpha$  and NF $\kappa$ B levels in all groups

Group	TNF- $\alpha$	NF- $\kappa$ B (ng/ml)
G1	506 $\pm$ 25 c	1.2 $\pm$ 0.06 c
G2	495 $\pm$ 23 c	1.3 $\pm$ 0.1 c
G3	477 $\pm$ 29 c	1.3 $\pm$ 0.1 c
G4	439 $\pm$ 27 c	1.0 $\pm$ 0.1 c
G5	2009 $\pm$ 105a	3.5 $\pm$ 0.1 a
G6	1521 $\pm$ 144 b	2.1 $\pm$ 0.3 b
G7	678 $\pm$ 62 c	2. $\pm$ 0.2 b
G8	512 $\pm$ 22 c	1.7 $\pm$ 0.1 c

Each value is given as the mean $\pm$  SEM. The statistical analysis was done by using one-way ANOVA followed by the Tukey test. G1: negative control group, G2:125mg/kg metformin group: G3: 250mg/kg metformin group, G4:500mg/kg metformin group, G5: positive control group (400mg/kg V.A), G6: 125mg/kg metformin + V.A, G7: 250mg/kg metformin + V.A, G8: 500mg/kg metformin + V.A. Different lower - case letters indicate a significant difference among groups.



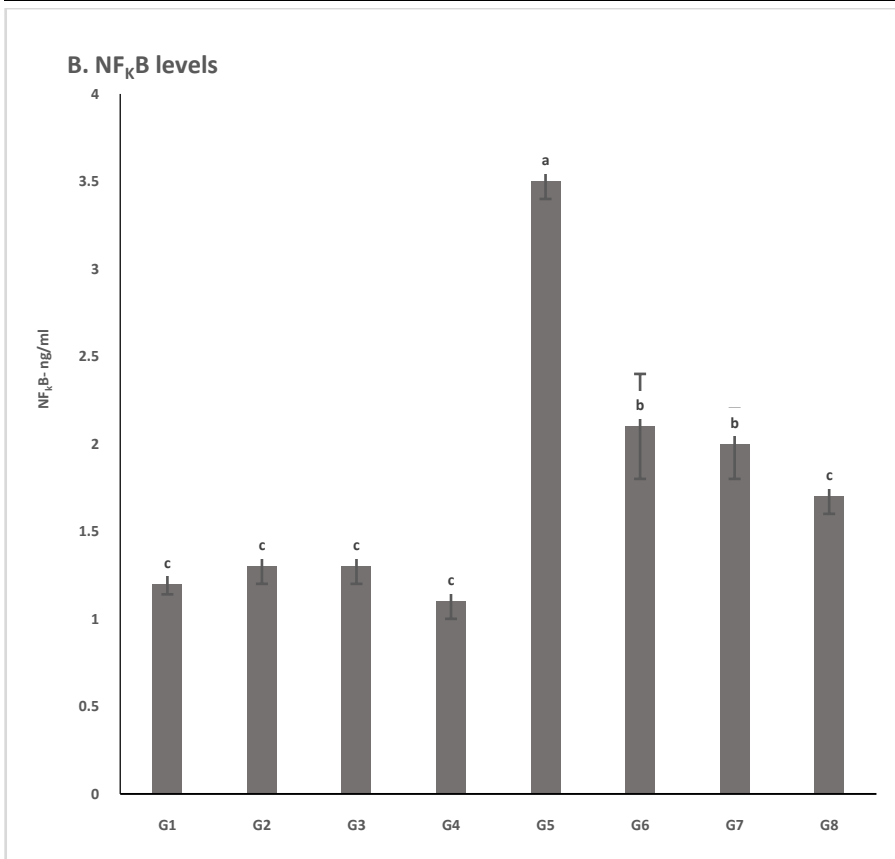


Figure 2. Effect of metformin on TNF- $\alpha$  and NF- $\kappa$ B levels in all groups

The results represented as mean  $\pm$  SEM. The statistical analysis was done by using one-way ANOVA followed by the Tukey test. G1: negative control group, G2: 125mg/kg metformin group, G3: 250mg/kg metformin group, G4: 500mg/kg metformin group, G5: positive control group (400mg/kg V.A), G6: 125mg/kg metformin + V.A, G7: 250mg/kg metformin + V.A, G8: 500mg/kg metformin + V.A. Different lower - case letters indicate a significant difference among groups.

### 3. Effect of Metformin at on Liver Histology of Rats Exposed to V.A

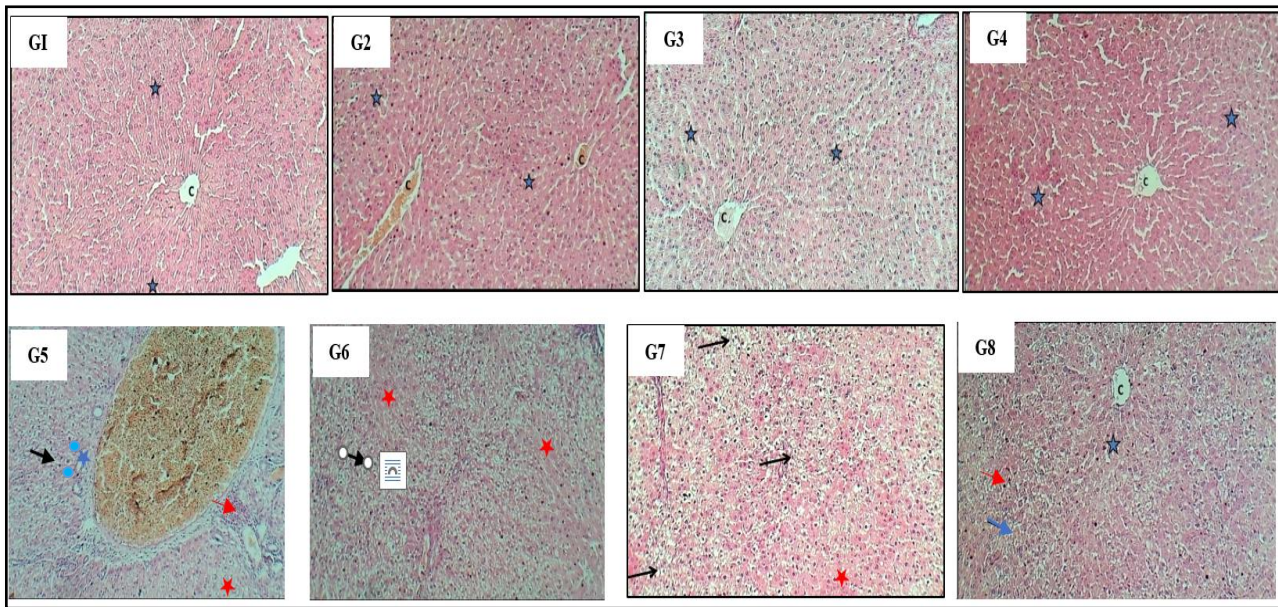
Following staining, the samples were examined under a light microscope at 100X magnification. Histologic studies shown that the group I (control) had normal central veins, sinusoids, and hepatocytes. Groups II, III, and IV alone receiving metformin showed normal hepatocytes and normal hepatic tissue spaces, similarly to the group I. Group V (receiving V.A) revealed significant alterations, including severe expansion of the sinusoid spaces, bile ductular proliferation, cellular swelling, inflammation and necrosis hepatocytes.

The microscopic in group VI (125 mg/kg metformin +V.A) did not reveal any improvement in morphologic alterations in hepatocytes when compared to the group V. In group VII (250g/kg +V.A), showed improvement including moderate venous dilation and congestion, moderate sinusoidal expansion, and mild focal cellular swelling and necrosis of the hepatocytes. group VIII (500 mg/kg metformin +V.A), found normal vascular elements, mild disarrangement of hepatic cords, sinusoidal dilatation and congestion with little generated hepatocytes and a few infiltrated mono nuclear leukocytes (figure 4, table 4).

### Discussion

In this study, the level of TAC in the groups I, II, and III is non-significant differences, but in group IV is slightly higher than group I. valproic acid (400mg/kg dose) showed a significant decrease in TAC serum levels as compared to control group, as shown in table (1) and figure (1). These findings can be attributed to chronic use of V.A has been linked to hepatocyte injury via the production of reactive oxygen species (ROS) as a result of metabolic activation and elevated oxidative stress.





**Figure 3.**Effect of metformin at on liver histology of rats exposed to V.A

G1: negative control group, G2:125mg/kg metformin group: G3: 250mg/kg metformin group, G4:500mg/kg metformin group, G5: positive control group (400mg/kg V.A), G6: 125mg/kg metformin + V.A, G7: 250mg/kg metformin + V.A, G8: 500mg/kg metformin + V.A.(Red arrow): mononuclear leukocytes infiltration; (black arrow): cellular swelling; (Blue asterisks):normal hepatocytes; (Red asterisks): necrosis; (blue cycle): bile ductular proliferation; (blue arrow): sinusoid dilated(Magnification: 100X, staining: H&E).

Indicated by a decrease in TAC levels. The results are in line with Omidipouret *al.* 2021<sup>(11)</sup>.Metformin (250 and 500 mg/kg doses) in combination with V.A significantly increased levels ofTAC when compared with the valproic acidgroup suggests metformin inhibition of mitochondrial complex I and the complex I may have a significant role in the formation of cellular ROS<sup>(9)</sup>.Previous research has focused on the antioxidant effect of metformin and lowered oxidative stress caused by various drugs such as thioacetamide. (Al-hashem *et al.* 2018)<sup>(12)</sup>, and methotrexate (Risk *et al.* 2018)<sup>(13)</sup>.

1705

**Table 3.**Histopathological alteration in all groups

Parameters	G1	G2	G3	G4	G5	G6	G7	G8
congestion	0	0	0	0	++ +	++ +	+ +	+
Hepatic necrosis	0	0	0	0	++ +	++ +	+ +	0
Hepatic fibrosis	0	0	0	0	0	0	0	0
Inflammatory cell	0	0	0	0	++ +	++ +	+ +	+
Hepatic sinusoidal dilation	0	0	0	0	++ +	++ +	+ +	+
Hepatic swelling	0	0	0	0	++ +	++ +	++ +	0

(-): none obvious damage; (+): mild hepatocellular lobules affected; (++) : moderate hepatocellular lobules affected; (+++): severe of hepatocellular lobules affected. G1: negative control group, G2:125mg/kg metformin group: G3: 250mg/kg metformin group, G4:500mg/kg metformin group, G5: positive control group (400mg/kg V.A), G6: 125mg/kg metformin + V.A, G7: 250mg/kg metformin + V.A, G8: 500mg/kg metformin + V.A.

An essential mechanism implicated in VPA-induced liver damage is the promotion of inflammatory cascades. NF- $\kappa$ B transcription factors, which bind to oxidative damage and inflammation, appear to be activated by oxidative stress<sup>(14)</sup>.In this study, the V.A group was shown to have significantly increased tumor necrosis factor-alpha (TNF- $\alpha$ ) production as shown in table (2) and figure (2.A) and stimulated nuclear factor-kappa B (NF- $\kappa$ B) expression as shown in table (2) and figure (2.B),these data concur with Abdelkaderet *al.* (2020) <sup>(5)</sup>outcomes, who also showed elevation in TNF-  $\alpha$ and NF $\kappa$ B levels with V.A. TNF-  $\alpha$  levels in the control group are slightly higher than in metformin groups, particularly at high metformin doses, which have the lowest TNF-  $\alpha$  and NF- $\kappa$ B values. the coadministration of metformin at dosage of 250 and 500 mg/kg/daywith V.A was resulted in significant decrease TNF- $\alpha$  this suggests that metformin inhibits a variety of mechanisms



involved in inflammation, including mTOR-related TNF- $\alpha$  and reducing NF-kB activation and phosphorylation of inhibitor of kappa B (I $\kappa$ B) by activated AMPK<sup>(15)</sup>. These results were in line with Junfeiet al. (2014)<sup>(10)</sup> and Dehkordi et al. (2018)<sup>(8)</sup> who found metformin inhibits the expression of proinflammatory cytokines by blocking NF- $\kappa$ B activation. Metformin through AMPK activation attenuate phosphorylation and subsequent degradation of I $\kappa$ B- $\alpha$  by inhibiting IKK activity, resulting in suppression of cytokine-induced NF-kB activation<sup>(10)</sup>. Several previous studies focused on the anti-inflammatory effects of metformin, like Vasamsettiet al. (2015)<sup>(16)</sup>, who found metformin via activated AMPK can effectively inhibit monocyte-to-macrophage differentiation and associated inflammatory pathways. Histopathological scoring (HPS) was used to assess liver damage in all groups, taking into account various factors. The scoring systems are composed of several histological features and indicate the level of hepatic injury. Low HPS values was found in metformin groups, whereas high HPS value was observed in valproic acid group. Higher HPS values suggest hepatic injury in valproic acid group. Whereas, low HPS value in metformin treated groups suggests antioxidative, and anti-inflammatory effect of metformin. Similarly, moderate HPS value was found in 250 dose metformin whereas low HPS value was showed in high doses of metformin figure (3), table (3). These finding supported by several of previous study like methotrexate Risket al (2018)<sup>(11)</sup> and Al-Hashem et al (2018)<sup>(10)</sup>.

## Conclusion

The administration of V.A. increased oxidative stress by lowering TAC serum levels. Orally administered metformin protects the liver from V.A toxicity by elevating the antioxidant capability and correcting the level of the proinflammatory cytokines as well as abnormal changes in the liver structure during V.A-induced liver injury.

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