Pathotoxic Effects of Arsenic Trioxide on Immunized and Infected Rats by *Salmonella typhimurium* and ameliorated by α- Lipoic Acid

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Abstract - The study was performed on 120 white rats of approximately of the same body weight (200-220gms) divided equally into 8 groups. 1st group immunized with WSSTAg subcutaneously (two doses at two weeks intervals). 2nd group was immunized with WSSTAg and supplemented with alpha lipoic acid (100 mg/kg BW intraperitoneally once daily for 30 days). 3rd group was immunized with WSSTAgs and received arsenic trioxide (1.5 mg/kg BW I/P once daily for 30 days). 4th group was immunized with WSSTAgs and supplemented with alpha lipoic acid, also it received arsenic trioxide. 5th group was treated as negative control group and it received only I/P 0.2 ml of PBS (I/P once daily for 30 days). 6th group (non immunized) was treated with arsenic trioxide alone (1.5 mg/kg B.W I/P once daily for 30 days). 7th group (non immunized) was treated with arsenic trioxide (1.5 mg/kg B.W I/P once daily for 30 days) and then inoculated with alpha lipoic acid (100 mg/kg B.W I/P once daily for 30 days). 8th group (non immunized) was inoculated with alpha lipoic acid alone (100 mg/kg B.W I/P once daily for 30 days).

After 30 days, the animals were immunized with WSSTAg and then after three days, all animals were infected experimentally with $1x10^8$ CFU/ml of *Salmonella typhimurium* as a challenge dose and continued for 10 days. Our results showed that there is severe histopathological changes in the liver of group 6th and control group (negative control), due to high virulence of *Salmonella typhimurium* strain and the immunosuppressive effect of ATO, whereas the results of groups which received alpha lipoic acid with immunization particularly 7th and 4th, were demonstrated less severity and mild lesions when compared with the group 6th and control group (5th).

Key words: ATO, *S. typhimurium*, ALA, rats.

I. Introduction

Arsenic (AS) is ubiquitous element in the environment. Weathering of rocks converts sulfides to arsenic trioxide, which enters the arsenic cycle as dust or by dissolution in rain, rivers, or ground water (Mandal and Suzuki, 2002). Arsenic is a very toxic metal, and also an environmental and industrial pollutant which is present in soil, water, air and food (Cullen, 1989).

This metal enters surface water from the industrial and found in soil by leaching of sewage sludge through soil (Antman, 2001). So, the population can be affected by arsenic through food consumption, drinking water and incidental ingestion of soil contaminated by arsenic (Celik *et al*., 2008). It is used in foods preservatives, herbicides, insecticides and rodenticides (Akter *et al*., 2005). Arsenic (As) is a widespread environmental toxin, it enters the organisms by dermal contact, inhalation, or ingestion of contaminated drinking water and affects nearly entire organ systems of the body (Ratnaike, 2003). Arsenic compounds are quite effectively incorporated from the gastrointestinal tract (Zielhuis and Wibowo, 1984). After absorption, It transports in the plasma is bound to albumin and accumulated mainly in kidney and liver. Arsenic occurs both organic and inorganic forms in nature but inorganic species of arsenic (AS^{III} and AS^{V}) represent a potential threat to the environment, human and animal health due to their carcinogenic and other effects (Singh *et al*., 2004). Arsenic trioxide is a trivalent inorganic compound (Saxena *et al*., 2008).

Arsenic can result in acute and chronic toxicity. The characteristics of chronic effects of arsenic toxicity are degenerative inflammatory and neoplastic changes of the skin, respiratory, haemopoitic, cardio vascular, nervous, hepatic, endocrine and renal system (Hughes, 2002). Also causes an oxidative stress through lipid peroxidation and consumption of some antioxidant systems (Yamauchi *et al*., 2004).

Previous studies showed that arsenic contamination may cause wide variety of diseases such as cancers, diabetes mellitus (Tseng *et al*., 2000), cardiovascular disorders (Das *et al*., 2004), reproductive toxicity (Ahmed *et al*., 2008) as well immunotoxicity (Soto- Peña *et al*., 2006).

Alpha lipoic acid (ALA) is a strong antioxidant that plays an essential role as a cofactor in the metabolism of all organisms (Navari-Izzo *et al*., 2002 ; Packer *et al*., 1995). It has been shown to exhibit antioxidant (Li *et al*., 2013), anti-inflammatory (Kwiecień *et al*., 2013), anti-toxicity of heavy metals especially against arsenic toxicity (Dwivedi *et al*., 2014), anti-carcinogenic activities (Kapoor, 2013), as well as immunomodulating activity (Ohmori *et al*., 1986 b).

The aim of study:

This study aimed to:

(USA). Using of effective dose according to the instructions of the drug and depending to Ahmed and Khan, (2012), who reported that 100 mg/kg B.W. of ALA used as effective dose in rat intraperitoneally.

LD50 calculation of arsenic trioxide:

LD50 of arsenic trioxide was 15mg/kg B.W which calculated by probet method (Klaassen, 2008).

Experimental design:

One hundred and twenty of white rats, both sexes were randomized into eight groups of (15) rats each group and were treated as following:

1st **group** was immunized with WSSTAgs, two doses, two weeks intervals subcutaneously. **2nd group** was immunized as in 1st group and at same time treatment with alpha lipoic acid (100 mg/kg B.W I/P). **3rd group** was immunized as in 1st group then treated with arsenic trioxide (1.5 mg/kg B.W I/P). **4th group** was immunized with WSSTAgs and then injected with arsenic trioxide and treated with alpha lipoic acid. **5nd group** (control group) was injected I\P 0.2ml with PBS (phosphate buffered saline). **6th group** (non immunized) was treated with arsenic trioxide alone (1.5 mg/kg B.W). **7th group** (non immunized) was treated with arsenic trioxide (1.5 mg/kg B.W) and then injected with alpha lipoic acid (100 mg/kg B.W). **8th group** (non immunized) was injected with alpha lipoic acid alone (100 mg/kg B.W).

After 30 days, the animals were immunized with WSSTAg and then

1- The sensitivity of animal models (rats exposed arsenic trioxide) post injection with a challenge dose of *Salmonella typhimurium.*

2- Using alpha lipoic acid to ameliorate the toxicity of ATO.

II. Materials and Methods

Experimental animals:

One hundred and twenty of white rats (200 – 220 gm) were obtained from animal house of Vet. Med. College of Al- Qadisiya University and prior to use. The animals were acclimatized for 7 days at 12 h light/dark cycle. The animals were housed in plastic cages in an air-conditioned room with temperature maintained at 25 ±2 C. Rats were given food pellets and water ad libitum. All rats were randomized into eight groups of 15 rats each and were treated for three months.

Chemicals:

Arsenic trioxide: this heavy metal was obtained from central laboratory in Al-Qadisiya University. Arsenic trioxide (As2O3, molecular weight 197.8) (AnalaR BDH chemical Ltd., Poole England). LD50 of arsenic trioxide by probet method (Klaassen, 2008) which was 15mg/kg B.W. The rats administered 1/10 of LD50 about (1.5mg/kg B.W) which is considered as chronic dose.

Alpha lipoic acid: it was procured from Al- Harithea pharmacy. The origin was Sigma Chemicals

III. Results and discussion

Histopathological changes in the liver sections post-injection of challenge dose of *Salmonella typhimurium*:

***5th group (as control group):**

This subgroup inoculated with challenge dose of *Salmonella typhimurium*. This 5th group showed histopathological changes but lesser than subgroup A6 in severity, and these changes were characterized by infiltration of inflammatory cells (polymorphonuclear cells) around central veins (as in figure (1) ; (2) ; (3) ; (4)), congestion of the central veins (as in fig. (3)). Also there is hyperplasia of bile ducts epithelium as in fig. (4).

All these changes which happened in this subgroup indicate the pathological aspect which occur due to inoculation of virulent strains of *Salmonella typhimurium* specially in the liver which considered a major target organ of the pathogen, this result agreed with Conlan, (1996), who indicated the histological examination in the livers challenged with $5X10^8$ CFU of Salmonella in mice.

Also these changes which occur in livers may be due to a possible breach in the integrity of the bile epithelium leading to leakage of an irritant, like bile, into the periportal connective tissues.

This evidence agreed with Zghair, (2012), who indicated the histopathological lesions which occur after three days, all animals were infected experimentally with $1x10^8$ CFU/ml of *Salmonella typhimurium* as a challenge dose and continued for 10 days. Then all the animals were sacrificed and (3 cm^3) pieces from the liver of the animals were taken for histopathology (Luna, 1968).

Preparation of whole sonicated *Salmonella typhimurium* Antigens (WSSTAgs):

Whole sonicated *Salmonella typhimurium* Antigens was prepared according to Mitove *et al*., (1992).

Bacterial isolate:

The isolate of *Salmonella typhimurium* was provided by the unit of Zoonotic Diseases/Veterinary Medicine College of AL-Qadisiya University. It was isolated from rats and diagnosed by the central public health laboratory/Ministry of Health. Then the bacterial isolate was prepared according to (Quinn *et al*., 1998).

Determination of the challenge dose of *S. typhimurium*:

Density of *Salmonella typhimurium* in the challenge dose was calculated by the densimeter (DensiCNEX) as 0.5 McFarland which equal $3x10^8$CFU/ml and diluted in 2ml of sterile saline to reach $1x10^8$CFU/ml.

as well as to chronic and opportunistic pathogens. Also Ferrario *et al*., (2009) indicated that arsenic at 1*m*M was able to decrease the telomerase mRNA and protein expression and telomere length enhancing the apoptotic pathway in a ROS dependent manner in human cord blood cells.

For all these reasons, the results demonstrated the severe histopathological changes in the liver sections post-inoculation with challenge dose of *Salmonella typhimurium* to the arsenic trioxide-exposed rats.

***7th group**: (Non-immunized group received arsenic trioxide and supplemented with alpha lipoic acid):

The histopathological changes in the liver sections of animals of this group showed nearly 4th group.

The lesions are characterized by mild or undetectable infiltration of inflammatory cells and presence of hepatic architecture and there is mild hyperplasia of bile ducts epithelium as in Fig. (11). these results indicate the beneficial and ameliorative effect of alpha lipoic acid for the toxicity of arsenic trioxide.

Arsenic trioxide will increase the susceptibility to infection and it can cause increase in the bacterial growth of *Salmonella typhimurium* in the rats challenged with virulent strain of these bacteria due to the immunosuppressive effect of arsenic trioxide which mentioned above in details.

Also Arsenic trioxide can produce high levels of reactive oxygen species in mice livers infected with $1X10^8$CFU of *Salmonella typhimurium*.

***6th group:**

The histopathological changes appeared with high severity in the 6th group and these histologic changes characterized by high mononuclear cells aggregation around the central veins and among the hepatic tissue as in figure (5) ; (6) ; (7) ; (8), also there is fatty infiltration as in figure (6) congestion of the blood vessels as in figure (7), and proliferation of Kupffer cells with hyperplastic lesion of the bile ducts epithelium as in figure (8) ; (9). Also there is there is suppurative lesion with cellular debris in the center and inflammatory cells infiltration mainly neutrophils as in figure (10).

The reason of these changes may be due to the toxic effect of arsenic trioxide on the inflammatory and phagocytic cells like granulocytes and macrophages and then resulting in increased the susceptibility to infection. Arsenic trioxide can cause immunotoxic effect due to increased incidence of phagocytic cells apoptosis via increase generation of oxygen reactive species (ROS) could be major mechanisms of arsenic-induced immunosuppression. For these reasons, the impairing of normal function of the immune system due to the exposure to arsenic trioxide may have been predisposed to bacterial infections.

These results agreed with Andres *et al*., (2005), who indicated the arsenic may induce damage to immune cells which impairs their ability to respond to transformed cells,

cellular NAD(P)H for it reduction to DHLA and thus lowering the cellular NAD(P)H\ $NAD(P)^+$ ratio.

3rd Group: (immunized group received arsenic trioxide and challenged with *Salmonella typhimurium*):

The histopathological changes are characterized by small aggregations of inflammatory cells with mild dilation of sinusoids as in Fig. (12).The reason of these results due to the immunotoxic effect of arsenic trioxide which resulting in immunosuppressive state in the exposed animals. The immunosuppression is the consequence of an inhibition of the host's immune response which leads to the impaired resistance against microbial infections. This evidence agreed with Ferrario *et al*., (2009) they reported that the possible occurrence of infectious diseases has not been extensively studied in human exposed to occupational or environmental chemicals that are immunosuppressive in animals.

The immunosuppressive effect of arsenic can be resulting from significant decrease in the T cell proliferation, due to a reduced levels of secreted cytokines by the T-cell (TNF-alpha, IFN-gamma, 1L-2, 1L-10, 1L-5 and 1L-4) and this exactly in agreement with Biswas *et al*., (2008), so that in this 3rd group, arsenic trioxide causes diminishing of immune response due to induction of apoptosis of immune cells resulting in increased the sensitivity to bacterial infection (*Salmonella typhimurium*) via inhibition of phagocytic activity of the due to the increase in the activity of NADPH oxidase which results in the production of reactive oxygen species like superoxide $O2^-$, H_2O_2 and OH^-.

Whereas the supplementation of alpha lipoic acid will give good results or response against these toxicity through the opposite action of alpha lipoic acid for the toxic effect of arsenic trioxide.

The beneficial effect of alpha lipoic acid is characterized by the immunomodulator effect of alpha lipoic acid in both cell-mediated and humoral immunity mentioned above subgroups in details and opposite the immunotoxic effect of arsenic trioxide. Also alpha lipoic acid can inhibit or prevent the generation of the reactive oxygen species which are formed due to the exposure to arsenic trioxide via decrease activation of NADPH oxidase which is an essential enzyme responsible for the formation of superoxide through activation of NADPH.

All these mechanisms of alpha lipoic acid will decline or ameliorate the toxicity of arsenic trioxide and reduce the histopathological changes in the liver sections of subgroup A7 animals. These results agreed with Chou *et al*., (2004), who indicated the arsenic trioxide can produce the reactive oxygen species through activation of NADPH oxidase. Also Li *et al*., (2013) mentioned that alpha lipoic acid can decrease oxidative stress via inhibition of reactive oxygen species formation. Roy *et al*., (1998) indicates that lipoate has been suggested to lower reductive stress in pathologies such as diabetes and ischemic injury by utilizing

microscopic changes characterized by few inflammatory cells aggregations, proliferation of Kupffer cells and presence of normal hepatic architecture as in Fig. (13) & (14).

The reason of these histological changes in the liver sections of this group as the following: At first, this group (4^{th}) is an immunized group (immunized with WSSTAgs), so that there is increase in the immunity of the rat body. At the same time, it received alpha lipoic acid which acts as immunomodulator which have the repairing action and it can be ameliorate the immunotoxicity of arsenic trioxide.

Alpha lipoic acid can play an important role to reduce the toxicity of heavy metals especially arsenic trioxide. This role is via the immunomodularor effect of alpha lipoic acid which enhances maintaining, proliferation and increase numbers of T-cells and finally increases the resistance against bacterial growth and decrease the susceptibility to infection.

These result agreed with Ziegler *et al*., (2006) who indicate that alpha lipoic acid can be immunomodulator. Also Ohmori *et al*., (1986) who showed that alpha lipoic acid can increase proliferation and increase number of T-cell.

Also alpha lipoic acid can ameliorate the immunotoxic effect of arsenic trioxide via their ability to raise glutathione levels. Previous studies have been demonstrated that arsenic trioxide can increase the amounts of free radicals and a deficiency of inflammatory cells like macrophages and finally, it results in all these histopathological changes. These results agreed with Harrison and McCoy, (2001) who indicate that arsenic-mediated apoptosis may lead to a diminished immune response in mice, rats Bustamante *et al*., (1997) and human Gonzales-Rangel *et al*., (2005). Also our results agreed with other studies like Dai *et al*., (1999), who showed arsenic is immunosuppressive and that it enhances susceptibility to infections through inhibiting the activity of macrophages. Some workers showed that chronic exposure to arsenic, in addition to its general toxicity and it's stimulation of many diseases, may affect lymphocytes, monocytes and macrophage activity in many mammals, resulting in immunosuppression Sakurai *et al*., (2006). Likewise, phagocytic activity of macrophages and other immune responses were found to be significantly reduced by arsenic exposure in birds Vodela *et al*., (1997). Also Bishayi and Sengupta, (2003) indicate that arsenic interferes with macrophage function decreasing adhesion, migration and phagocytic properties.

***4^{th} Group:** (immunized group received arsenic trioxide and supplemented with alpha lipoic acid):

In this group, our results demonstrated the histopathological changes of the liver sections of this group animals were less than the histopathological changes those occurred in 3^{rd} group. These

sections, there is normal hepatic architecture except some mild congestion of the central veins as in Fig. (15) ; (16) in group 1st and 2nd and mild dilation of sinusoids with few scattered inflammatory cells which showed in 8th group as in Fig. (17) ; (18) . The reason of this may be due to these groups (1st, 2nd and 8th) were not received the immunosuppressive agent (arsenic trioxide), also because of elevation in the immunological state of the animals specially 2nd group which immunized with WSSTAgs and then supplemented with alpha lipoic acid. This increasing in the immunological levels result in decreased or inhibiting the bacterial growth and then reduce or diminish the histological changes in the liver sections of the animal of these subgroups. These results agreed with Kwiecien *et al.,* (2013) who indicate the anti-inflammatory properties of lipoic acid metabolites.

glutathione. Glutathione is necessary for regulating immune system T-cell activation and phagocytosis. Alpha lipoic acid has the ability to increase glutathione levels so that rising of glutathione levels has also been shown to maintain and activation of Th1 immune response, then increase the resistance to infection.

This suggestion indicates the indirect antibacterial activity of alpha lipoic acid. These results agreed with Naseem Ullah *et al.,* (2012) who indicate that arsenic trioxide can be decreased the levels of glutathione. Also Shay *et al.,* (2009) indicate that alpha lipoic acid can be increase the levels of glutathione, while Ghezzi, (2011) showed the role of glutathione in immune system.

***1st group, 2nd group and 8th group:**

All the 1st group, 2nd group and 8th group showed no or undetectable histopathological changes in the liver

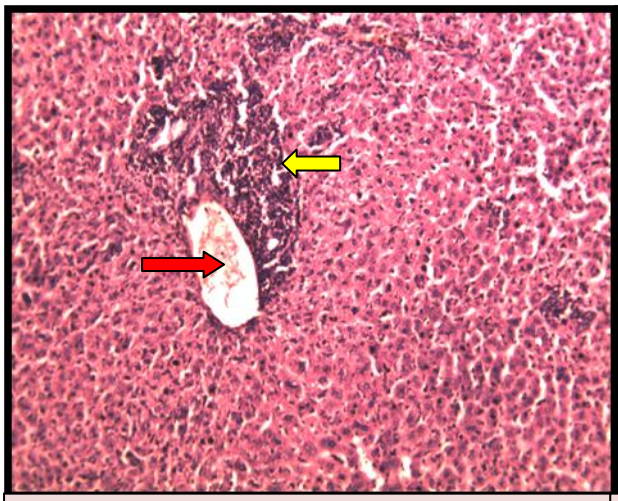

Figure (1): Liver section of rat as negative control (5th group). Injected experimentally with 1x10^{8}CFU/ml of *S. typhimurium* I/P. Note there is infiltration of inflammatory cells (yellow arrow) with congestion of central veins (red arrow). Also there is loss of hepatic architecture. 10X H&E.

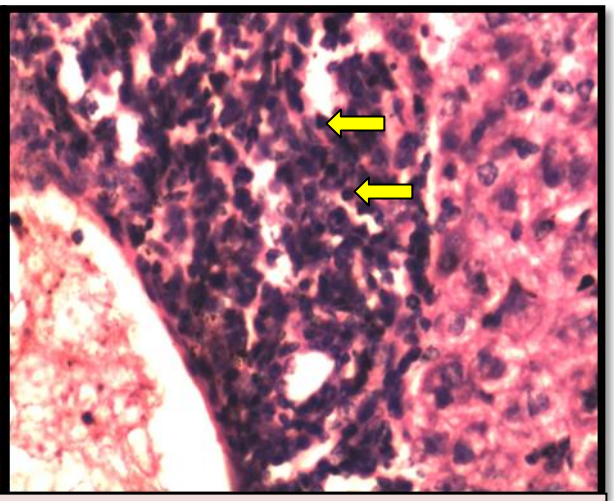

Figure (2): Liver section of rat as negative control (5th group). Injected experimentally with 1x10^{8}CFU/ml of *S. typhimurium* I/P. Higher magnification. Note there is infiltration of inflammatory cells mainly macrophages (yellow arrows), lymphocytes as well as neutrophils. Also there is loss of hepatic architecture. 40X H&E.

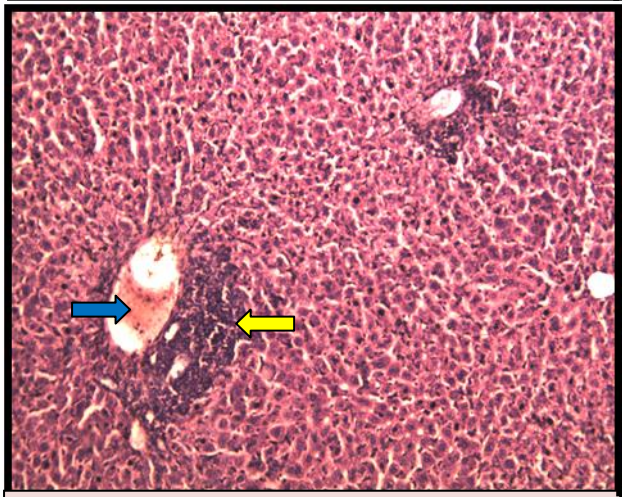

Figure (3): Liver section of rat as negative control (5th group). Injected experimentally with 1x10^{8}CFU/ml of *S. typhimurium* I/P. Note there is high infiltration of inflammatory cells (yellow arrow) with congestion (blue arrow) in the central veins. Also there is loss of hepatic architecture. 10X H&E.

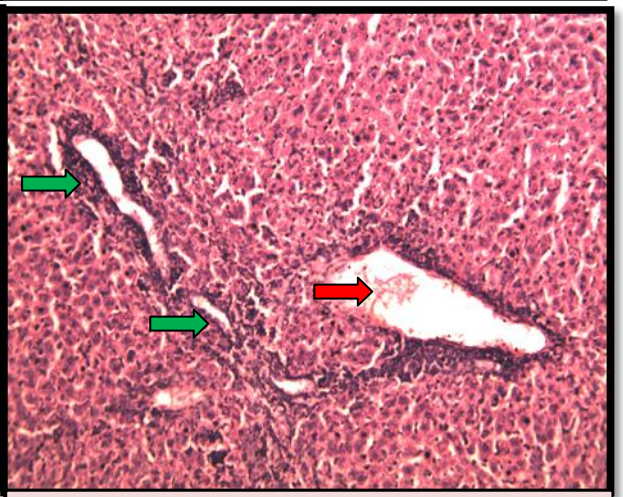

Figure (4): Liver section of rat as negative control (5th group). Injected experimentally with 1x10^{8}CFU/ml of *S. typhimurium* I/P. Note there is infiltration of inflammatory cells with congestion of central veins (red arrow). Also there is hyperplasia of the epithelial cells which lining of bile ducts (green arrows). 10X H&E.

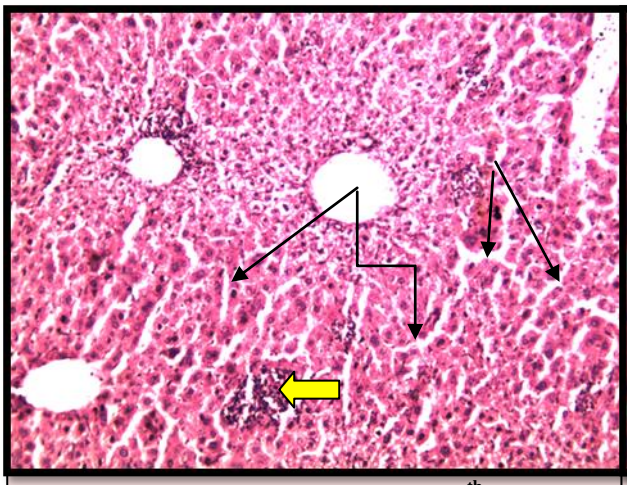

Figure (5): Liver section of rat in 6th group. It received arsenic trioxide (ATO) (I/P 1.5mg/kg BW) and then injected experimentally with 1x10^{8}CFU/ml of *S. typhimurium* I/P. Note there is infiltration of inflammatory cells (yellow arrow) with vacuolated hepatocytes and dilation sinusoids (thin arrows). 10X H&E.

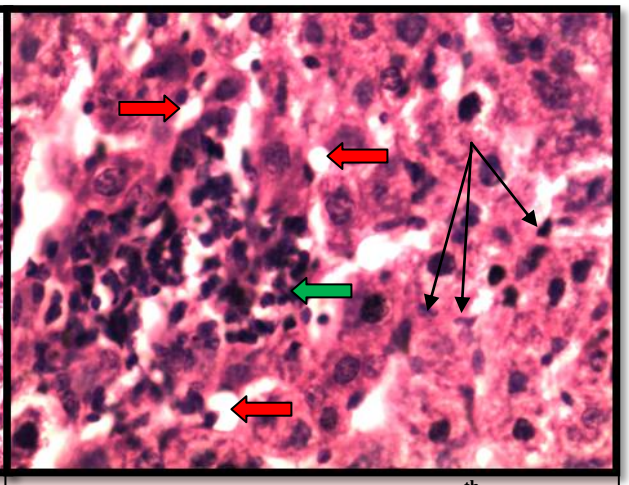

Figure (6): Liver section of rat in 6th group. It received ATO(I/P 1.5mg/kg BW) and then injected experimentally with 1x10^{8}CFU/ml of *S. typhimurium* I/P. Note there is infiltration of inflammatory cells (green arrow) with fatty infiltration (hepatocytes showed as a signet - like shape) (red arrows) and there is proliferation of Kupffer cells with dilation sinusoids (thin arrows). 40X H&E.

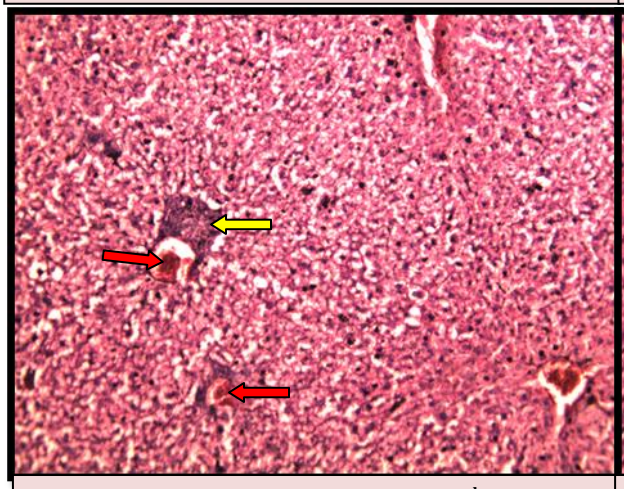

Figure (7): Liver section of rat in 6th group. It received ATO (I/P 1.5mg/kg BW) and then injected experimentally with 1x10^{8}CFU/ml of *S. typhimurium* I/P. Note there is infiltration of inflammatory cells and congestion of central veins (red arrow) with vacuolated hepatocytes and marked necrosis of hepatocytes. 10X H&E.

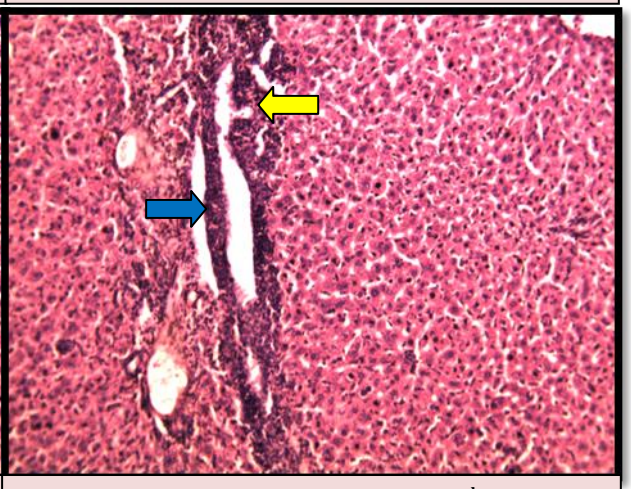

Figure (8): Liver section of rat in 6th group. It received ATO (I/P 1.5mg/kg BW) and then injected experimentally with 1x10^{8}CFU/ml of *S. typhimurium* I/P. High infiltration of inflammatory cells (yellow arrow) with hyperplasia of the epithelial cells which lining of bile ducts (blue arrow). 50X H&E.

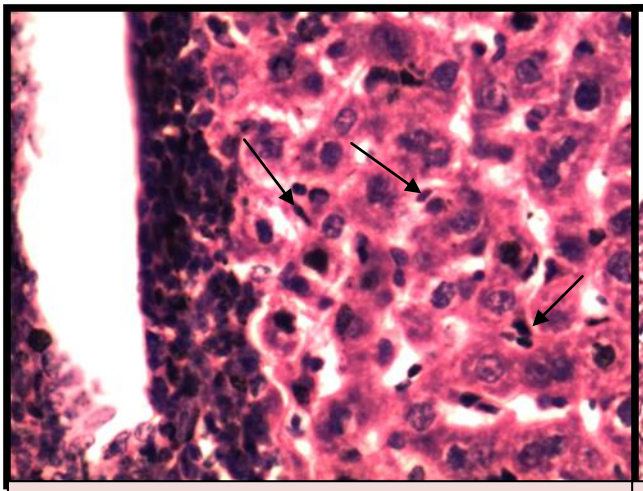

Figure (9): Liver section of rat in 6th group. It received ATO (I/P 1.5mg/kg BW) and then injected experimentally with 1x10^{8}CFU/ml of *S. typhimurium* I/P. Higher magnification. Note there is loss of hepatic architecture. Hyperplasia of the epithelial cells which lining of bile ducts and proliferation of Kupffer cells (thin arrows). 40X H&E.

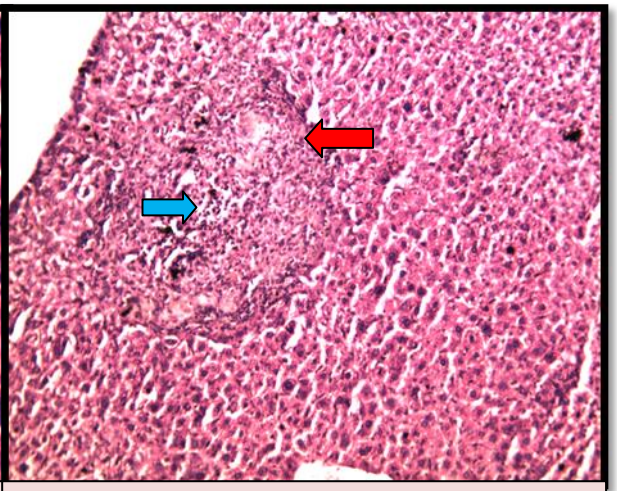

Figure (10): Liver section of rat in 6th group. It received ATO (I/P 1.5mg/kg BW) and then injected experimentally with 1x10^{8}CFU/ml of *S. typhimurium* I/P. Note there is suppurative lesion (red arrow) with cellular debris in the center (blue arrow) and inflammatory cells infiltration. 10X H&E.

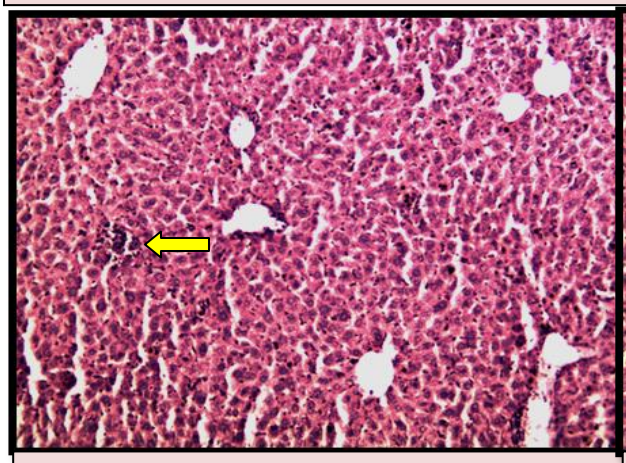

Figure (11): Liver section of rat in 7th group. It received ATO (I/P 1.5mg/kg BW) and supplemented with ALA (I/P 100mg/kg BW) and then injected experimentally with 1x10^{8}CFU/ml of *S. typhimurium* I/P. Note there is mild infiltration of inflammatory cells (yellow arrow) with presence of hepatic architecture. 10X H&E.

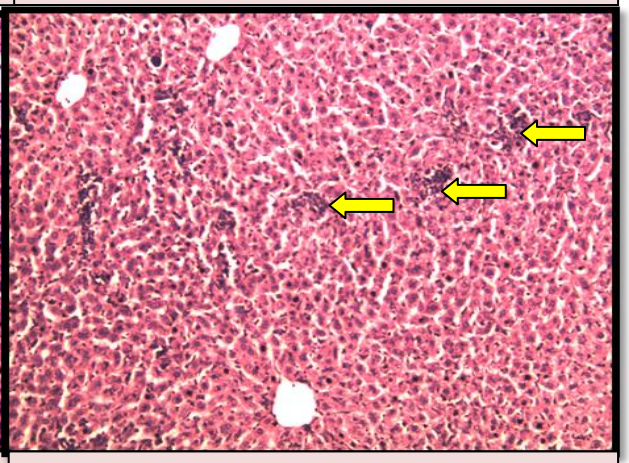

Figure (12): Liver section of rat in subgroup (A3). Immunized with WSSTAgs and it received ATO (I/P 1.5mg/kg BW) and then injected experimentally with 1x10^{8}CFU/ml of *S. typhimurium* I/P. Note there is inflammatory cells aggregations (yellow arrows), with loss of hepatic architecture. 10X H&E.

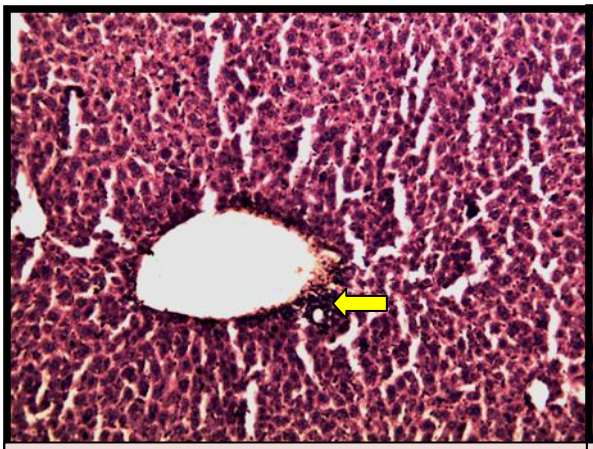

Figure (13): Liver section of rat in 4th group. Immunized with WSSTAgs and it received ATO (I/P 1.5mg/kg BW) and supplemented with ALA (I/P 100mg/kg BW) and then injected experimentally with 1x10^{8}CFU/ml of *S. typhimurium* I/P. Note there is very few inflammatory cells aggregations (yellow arrow) with presence of hepatic architecture. 10X H&E.

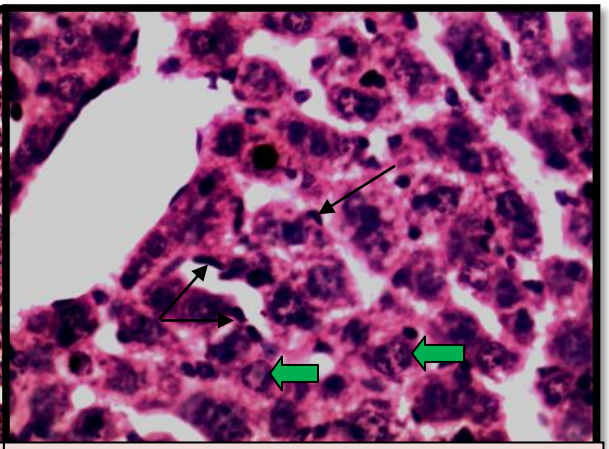

Figure (14): Liver section of rat in 4th group. Immunized with WSSTAgs and it received ATO (I/P 1.5mg/kg BW) and supplemented with ALA (I/P 100mg/kg BW) and then injected experimentally with 1x10^{8}CFU/ml of *S. typhimurium* I/P. Note there is normal hepatocytes (green arrows) with proliferation of Kupffer cells and presence of hepatic architecture (thin arrows). 40X H&E.

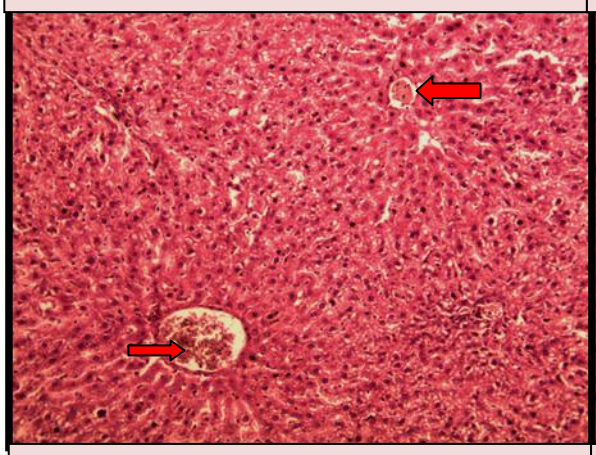

Figure (15): Liver section of rat in 1st group. Immunized with WSSTAgs and then injected experimentally with 1x10^{8}CFU/ml of *S. typhimurium* I/P. Note there is normal hepatic architecture in which the hepatocytes arranged radially around the central veins, there is mild congestion of the central veins (red arrow). 10X H&E.

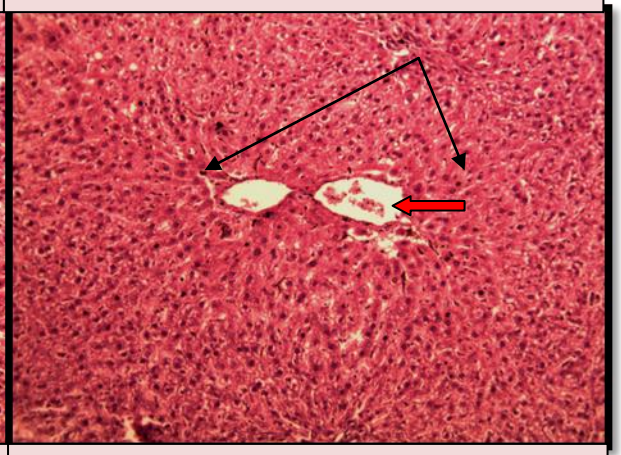

Figure (16): Liver section of rat in 2nd group. Immunized with WSSTAgs and supplemented with ALA (I/P 100mg/kg BW) and then injected experimentally with 1x10^{8}CFU/ml of *S. typhimurium* I/P. Note there is normal hepatocytes and hepatic architecture in which the hepatocytes arranged radially around the central veins (thin arrow), except some mild congestion of the central veins (red arrow). 10X H&E.

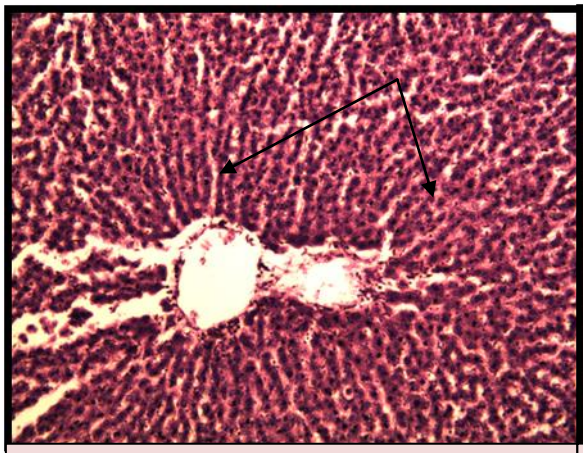

Figure (17): Liver section of rat in 8th group. Supplemented with ALA (I/P 100mg/kg BW) and then injected experimentally with 1x10^{8}CFU/ml of *S. typhimurium* I/P. Note there is normal hepatocytes and hepatic architecture in which the hepatocytes arranged radially around the central veins (thin arrows), very few scattered inflammatory cells and mild dilation of sinusoids. 10X H&E.

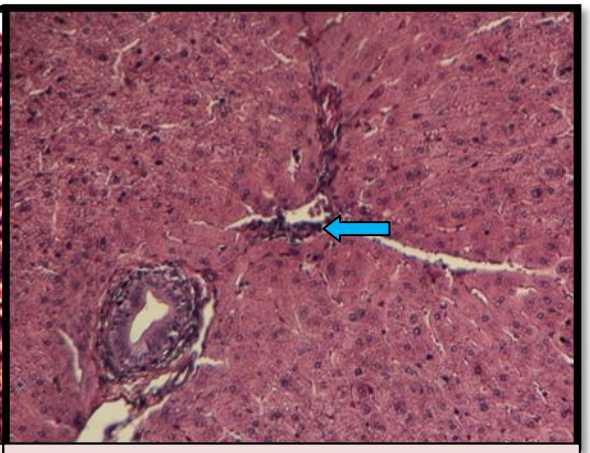

Figure (18): Liver section of rat in 8th group. Supplemented with ALA (I/P 100mg/kg BW) and then injected experimentally with 1x10^{8}CFU/ml of *S. typhimurium* I/P. Note there is normal hepatocytes and hepatic architecture, with mild infiltration of inflammatory cells (blue arrow) and mild dilation of sinusoids (thin arrows). 10X H&E.

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التغيرات المرضية السمية لثالث أوكسيد الزرنيخ على الجرذان الممنعة والمصابة بالسالمونيلا تايفيميوريم والتخفيف بواسطة حامض الفا ليبويك.

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الخلاصة

أجريت الدراسة على 120 جرذ أبيض من نفس وزن الجسم 200 – 220 غم مقسمة بالتساوي إلى (8) مجموعات على النحو التالي:

المجموعة الأولى مُنِعَتْ فقط بالمستضد الكلي المتكسر لجرثومة السالمونيلا تايفيميوريم تحت الجلد جرعتين على فترة أسبوعين لمدة 30 يوما. المجموعة الثانية مُنِعَتْ بالمستضد الكلي المتكسر لجرثومة السالمونيلا تايفيميوريم وحُقِنَتْ مع حمض ألفا ليبويك 100 ملجم /كجم من وزن الجسم داخل البريتون مرة واحدة يوميا لمدة 30 يوما. المجموعة الثالثة مُنِعَتْ بالمستضد الكلي المتكسر لجرثومة السالمونيلا تايفيميوريم وأُعطيتْ ثالث أكسيد الزرنيخ 1.5 ملجم /كجم من وزن الجسم داخل البريتون مرة واحدة يوميا لمدة 30 يوما. المجموعة الرابعة بالإضافة إلى تحصينها بالمستضد الكلي المتكسر لجرثومة السالمونيلا تايفيميوريم وتم أعطائها حمض ألفا ليبويك، و ثالث أكسيد الزرنيخ داخل البريتون مرة واحدة يوميا لمدة 30 يوما. المجموعة الخامسة هي مجموعة السيطرة، فقد أُعطيتْ فقط 0.2 مل داخل البريتون من المحلول الدارئ المتعادل داخل البريتون مرة واحدة يوميا لمدة 30 يوما. المجموعة السادسة غير مُمَنَعة وتم أعطائِها ثالث أكسيد الزرنيخ 1.5 ملجم/كجم من وزن الجسم داخل البريتون مرة واحدة يوميا لمدة 30 يوما. المجموعة السابعة غير مُمَنَعة تم أعطائِها ثالث أكسيد الزرنيخ 1.5 ملجم/ كجم من وزن الجسم ثم أعطيتْ حمض ألفا ليبويك 100 مجم/كجم من وزن الجسم داخل البريتون مرة واحدة يوميا لمدة 30 يوما. المجموعة الثامنة غير مُمَنَعة تم أعطائها حمض ألفا ليبويك فقط 100 مجم/كجم من وزن الجسم داخل البريتون مرة واحدة يوميا لمدة 30 يوما.

بعد مرور 30 يوما، جميع الحيوانات مُنِعُتْ بالمستضد الكلي المتكسر لجرثومة السالمونيلا تايفيميوريم ، وبعد ثلاثة أيام، جميع حيوانات أصيبت تجريبيا بواسطة ($10x1^8$ خلية/مل) من السالمونيلا تايفيميوريم كجرعة تحدي واستمرت لمدة 10 يوما، ثم تم نبذ الحيوانات واخذ 3 $سم^3$ من الأكباد التقطيع النسيجي. أظهرت نتائجنا أيضا أن هناك تغيرات نسجية مرضية شديدة في أكباد المجموعة السادسة ومجموعة السيطرة بسبب ضراوة السالمونيلا تايفيميوريم العالية والتأثير المثبط للمناعة بسبب ثالث أكسيد الزرنيخ،

في حين أن المجموعات التي حصلت على حمض ألفا ليبويك (السابعة) أو مع التحصين (الرابعة) أظهرت نتائج أقل شدة والآفات كانت خفيفة بالمقارنة مع المجموعة السادسة ومجموعة السيطرة.