BIOLOGICAL STUDIES OF THE EFFECT OF SOME NEW SYNTHETIC TRIAZOLE DERIVATIVES ON EHRLICH ASCITES CARCINOMA CELLS.

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ABSTRACT:

The importance of triazole derivatives lies in the fieldof organic or pharmaceutical chemistry that they have occupied a unique position in heterocyclic chemistry, due to its various biological activities. The aim of our study is to determine the bioactivity (evaluation of the anti-tumor and anti-oxidant activity) of the following trizole derivatives: **(S19)**7-(benzylamino)-2-(ethylthio)-6-formyl-5-oxo-1-phenyl-1,5-dihydro-[1,2,4] triazolo [1,5-a]pyridine-8-carbonitrile and **(S18)**2-(ethylthio)-6-formyl-7-(isobutylamino)-5-oxo-1-phenyl-1,5-dihydro-1,2,4 triazolo [1,5-a] pyridine-8-carbonitrile.

Materials & Methods: The new synthesized compounds will be investigated for their toxicityand applied on an experimental carcinogenesis model in order to evaluate its antitumor potential and anti-oxidant effect; against animal carcinogenesis "Ehrlich carcinoma)" (EAC).

Results: It was found that S91 & S18 were safe compounds; also these compounds increase life span of treated animals. Administration of S91 (5mg/kg I.P.) and S18 (5 mg/kg, I.P) results in a significant reduction in the volume of EAC by 59% and 64% and in the count of EAC cells by 34% and 47% in S91 and S18 treated groups; respectively. An anti-oxidant effect of S91 and S18 *in vivo* was observed; the results investigate a significant decrease in malodialdehydeby66.66% & 71.6%& interlukin-6 levels by 6.8% & 23% in S91 and S18 treated groups; respectively compared to positive control group. While, results showed a significant increase in super oxide dismutase activity, catalase activity, and glutathione reduced levels. While these compounds showed hepatotoxicity which indicated that by an increases in ALT and AST activities, and slight changes in kidney functions.

Conclusion: Triazole is a unique template that is associated with several biological activities. The anti-tumor mechanisms may be mediated by preventing oxidative damage and improved animal chances of survival. The results of clinical trials will be needed to spur the development of triazole derivatives as cancer therapeutic agents.

KEY WORDS:

Triazole
Ehrlich ascites carcinoma cells
Oxidative stress
Antioxidants.

INTRODUCTION:

Cancer is a disease process which may affect multicellular organisms and which is characterized by the uncontrolled multiplication and is able to invade other tissues[1]. The chemistry of heterocyclic compound continues to be an explore field in the organic or Pharmaceutical chemistry.

The importance of triazole derivatives lies in the field that they have occupied a unique position in heterocyclic chemistry, due to its various biological activities[2]. Triazole refers to either one pair of isomeric chemical compound having membered ring of two carbon atom and three nitrogen atoms. The two isomers are 1, 2, 3 triazole and 1,

2, 4 triazole. 1, 2, 4-triazolo [1, 5-a] pyridines and azolotriazolopyridines ring systems. The products were screened for various types of activity like antibacterial, anti-fungal and antioxidative activity[3]. The derivatization of Triazole ring is based on the phenomenon of bioisosterism in which replacement of oxygen of oxadiazole nucleus with nitrogen triazole analogue. Out of the two triazoles 1, 2, 4- triazole has wide variety of activity[4]. The aim of our study is to evaluateAntitumor activity and antioxidant status of 7-(benzylamino)-2-(ethylthio)-6-formyl-5-oxo-1-phenyl-1,5-dihydro-[1,2,4] thiazole [1,5-a] pyridine-8-carbonitrile (S19) and 2-(ethylthio)-6-formyl-7-(isobutylamino)-5-oxo-1-phenyl-1,5-dihydro-1,2,4] triazolo[1,5-a] pyridine-8-carbonitrile (S18); against Ehrlich ascites carcinoma (EAC) tumor in mice.As, triazoles are safe for most patients; their use in medically complex cases can be complicated further by dose-limiting toxicities and pharmacokinetic drug-drug interactions[5]. It was considered as triazole derivatives act as free radical scavengers and antioxidants, inhibiting lipid peroxidation and oxidative DNA damage, with abilities to inhibit activation of NF-κB. Based on various experimental and theoretical results it is definitely concluded that the phenolic (-OH) plays a major role in the activity of triazole derivatives[6]. One possibility is that the NF-κB transcription factor turns on transcription of the IL-6 gene. Anticancer drugs designed to block chromosome functioning may work much more effectively than targeted anticancer medicines that block the cytoplasmically located signaling pathways toward protein synthesis (cell growth)[7]. Hepatotoxic reactions are among the most common, and potentially serious, adverse effects associated with triazole therapy. The mechanism of hepatotoxicity is classified typically according to liver function test results, although liver biopsy may be required to confirm the diagnosis. Reactions resulting in degeneration or necrosis of hepatocytes (hepatocellular injury) typically manifest with significant elevations (>3-fold) in serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) concentrations. Occasionally, triazole therapy may be associated with a mixed pattern of liver injury (hepatotoxic and cholestatic)[8].

MATERIALS AND METHODS:

Animals: 180 Female Swiss albino mice of 8 weeks of age, weighed 22 to 25g body weight were housed at the experimental animal house of the faculty of Science, Zagazig University. The animals were maintained in controlled environment of temperature, humidity and light. They were fed on a commercial standard diet and tap watered libitum.

Tumors: Ehrlich ascites carcinoma (EAC) was initially supplied by the National Cancer Institute, Cairo, Egypt, and maintained in female Swiss albino mice through serial intraperitoneal (I.P) inoculation at 8 or 10 day intervals in our laboratory in an ascites form.

Chemicals: New synthetic compounds S91 (7-(benzylamino)-2-(ethylthio)-6-formyl-5-oxo-1-phenyl-1,5-dihydro-[1,2,4] triazolo[1,5-a] pyridine-8-carbonitrile) and S18 (2-(ethylthio)-6-formyl-7-(isobutylamino)-5-oxo-1-phenyl-1,5-dihydro-[1,2,4] triazolo [1,5-a]pyridine-8-carbonitrile) were synthesized in faculty of medicine, Minia University *(given as a gift from Prof. Dr. Khodair).*

Methods:

(I) Toxicity studies: Approximate LD_{50} of S91 and S18 in mice were determined according to method Reed and Muench[9].

(II) Dose response curve: Dose response curve of S91 and S18 in mice was determined according to method Crump et al.,[10].

Experimental design: 70 female albino Swiss albino mice were divided into 7 groups each one contains of 10 mice: Group I "served as negative control"; received saline solution; Group II "served as positive control; injected with $2.5x10^6$of EAC cells. Group III "S91 therapeutic group, injected with 5 mg/kg one day after EAC injection and repeated dose of S91 day after day; Group IV "S18 therapeutic group", injected with 5mg/kg one day after EAC injection and repeated dose of S18 injected day after day. Group V"DMSO group", injected with DMSO solution. Group VI" served as positive drug S91"; injected with 5 mg/kg day after day, and Group VII "served as Positive drug S18": injected with5 mg/kg day after day.

After the experiment, the blood samples and EAC cells were collected from mice for determination liver functions, kidney functions,IL-6, anti-oxidants assays, and viability study. Also, liver and kidney tissues were collected from animals for histological study.

Cell Viability and Counting of EAC cells: the viability of EAC cells was determined by the Trypan Blue Exclusion Method[11], where the total and viable cells (non-stained) were counted at magnification ×40; as the number of cells/ml was determined in the studied groups.

Estimation of Malondialdehyde (MDA) in Serum: the lipid peroxidation products were estimated by the formation of thiobarbituric acid (TBA) and quantified in term of MDA where, thiobarbituric acid (TBA) reacts with MDA in acidic medium at temperature of 95°C for 30 min to form thiobarbituric acid reactive product, the absorbance of the resultant pink product can be measured at 534 nm in a spectrophotometer[12].

Assessment of catalase enzyme activity (CAT): In the presence of hydrogen peroxides remaining H_2O_2 reacts with 3.5 -dichloro-2 hydroxy benzene sulfonic acid (DHBS) and 4-amino phenazone (AAP) to from achromophore with color intensity inversely proportional to amount of catalase in the original sample[13].

Assessment of Suproxid Dismutase (SOD): This assay relies on the ability of the enzyme to inhibit the phena-zinemetho sulphate-mediated reduction of nitrobluetetrazolium dye[14].

Assessment of Reduced glutathione (GSH):The method is based on the reduction of 5.5 dithiobis 2- nitro-benzoic acid (DTNB) with glutathione (GSH) to produce a yellow color the reduced chromogen is directly proportional to (GSH) concentration and its absorbance can be measured at 405 nm[15].

Liver Function tests: serum samples were screened for liver function tests including ALT, AST, total protein, and albumin according to the methods Schumann et al.,[16] Karmen et al,[17], Koller,[18] and Webster,[19] respectively.

Kidney function tests: serum samples were screened for kidney function tests including urea and creatinine

according to the methods Patton and Crouch,[20] and Murray,[21] respectively.

Determination of IL-6 using ELISA: IL-6 antigen was determined by enzyme-linked immunosorbent assay (ELISA) using a commercially available kit from Promocell (Heidelberg, Germany) according to the method of Isomura et al.,[22].

STATISTICAL ANALYSIS:

Statistical analysis was performed using SPSS software II version 14[23]. The effect of each parameter was assessed using the one way analysis of variance. Individual differences between groups were examined using Dunnett's test and those at $p<0.05$ were considered statistically significant.

RESULTS:

Determination of median lethal dose (LD_{50}) of S91& S18 compound: the acute toxicity LD_{50} was estimated by I.P. administration of S91 and S18; all doses indicate good safety; that suggests that S91 and S18 may be safe compounds.

Dose-response curve: it was cleared that 5 mg /kg mice was found to be the most effective dose as this dose reduced the number of EAC cells in S91 treated group by 37%; and by 47% for compound S18 treated group compared to positive control mice group, Fig. (1).

Viability, Counting of EAC cells and Life span: as to compounds S91 and S18; Table (I) summarizes their effects on EAC cells volume and count. The mean volume of EAC in the positive control group was found to be 4.2 ±0.5 (ml) as reported by Amer,[24]. This value was significantly decreased by 59.5%, and by 64.3%, ($p<0.01$) in S91& S18 treated groups; respectively.

Also, the mean count of EAC cells in the positive control group was found to be 126.52± 12.13 ($\times 10^6$), which significantly decreased by 34.7% and 47.9%, ($p<0.01$) in S91& S18 treated groups; respectively, compared to the positive control group, Fig (2).

S91 and S18 compound showed a significant increase in the life span prolongation to 25 days and 28 days by 78% and 100%; respectively compared to the positive control group.

Anti-oxidant Activity of S91 and S18 compounds: Table (II) and Fig. (3) illustrated anti-oxidant activity of S91 & S18. SOD activity, CAT activity and GSH levels was significantly increased in S91 and S18 treated groups by (275% and 80.1%, 360% and 900%, and 206.5% & 77.2%) ($p<0.001$) respectively; compared to the positive control group.

Effect of S91 and S18 on MDA and IL-6 levels: the mean MDA levels were significantly increased 28.5±4.9 (nmol/ml) in the positive control group compared to the negative control group 11.5±2.1 (nmol/ml) ($p<0.01$). Meanwhile, MDA levels showed a significant decrease in S91 and S18 treated groups by 66.6%, ($p<0.01$) and by 71.6%; ($p<0.01$); respectively compared to the positive control group. Also, IL-6 levels were significantly decreased in S91 and S18 treated groups by 6.8% and 5.6% ($p<0.01$); respectively, table (III, IV) and Fig. (4, 5).

Liver function tests: ALT & AST activity were significantly increased in positive control group by 54.7%, 26.2%, ($p<0.01$); respectively compared to negative control group; while no significant difference in total protein and albumin levels. On the

other hand; ALT & AST activity were highly significant increase in *S91*&*S18* by 145.3, 98%, and 203%, 129% ($p<0.001$); respectively; without significant difference in total protein and albumin levels compared to negative control group. Also in drug groups showed a slightly increase in the ALT & AST activities; while DEMSO group showed no significant difference ($p>0.01$) in all liver functions as illustrated in table (V, VI) and Fig.(6) [a, b].

Kidney function tests: Urea and creatinine levels were increased in the positive control by 106% and 95%; respectively ($p<0.01$)compared to negative control group. Meanwhile, *S91* treated group showed a non-significant difference in urea and creatinine levels ($p>0.01$)compared to negative control group. While, *S18* treated group showed a slightly increase in urea and creatinine by 33% and 50% compared to negative control. There was no a significant difference in urea and creatinine levels in the drug and DEMSO groups ($p>0.01$) compared to negative control group; table (VII, VIII) and Fig. (7) [a, b].

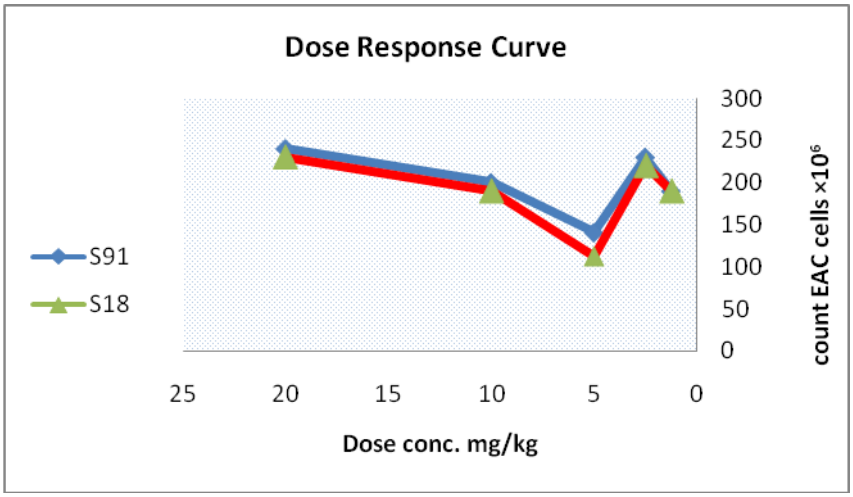

Fig. (1): Dose response curve for compound S91 & S18

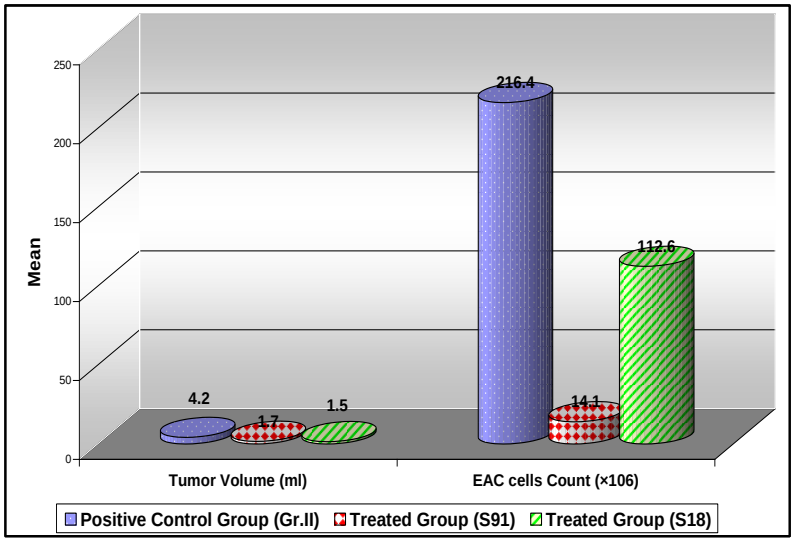

Fig. (2): Compound (S91) & (S18) effect on volume and count of tumor cells.

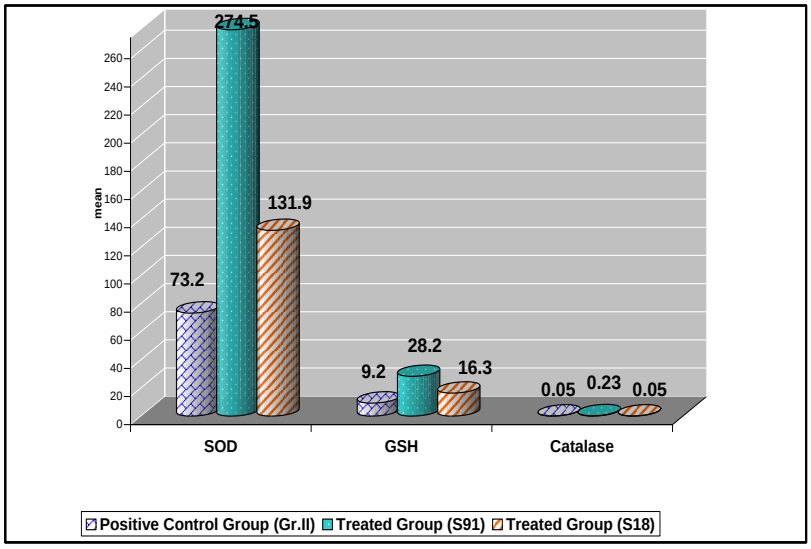

Fig. (3): Compound (S91) & (S18) effect on anti-oxidants "SOD, GSH, Catalase" in EAC cells.

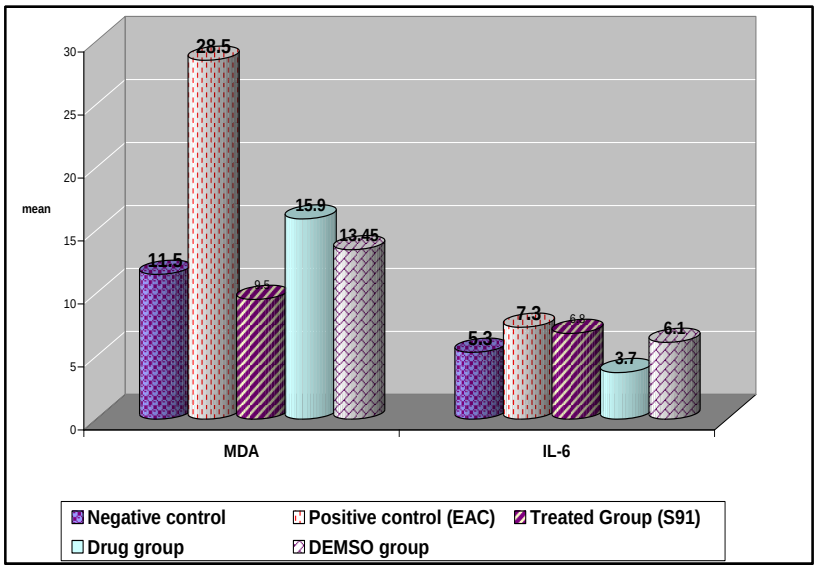

Fig. (4): Effect of Compound (S91) on MDA and IL-6 in all groups.

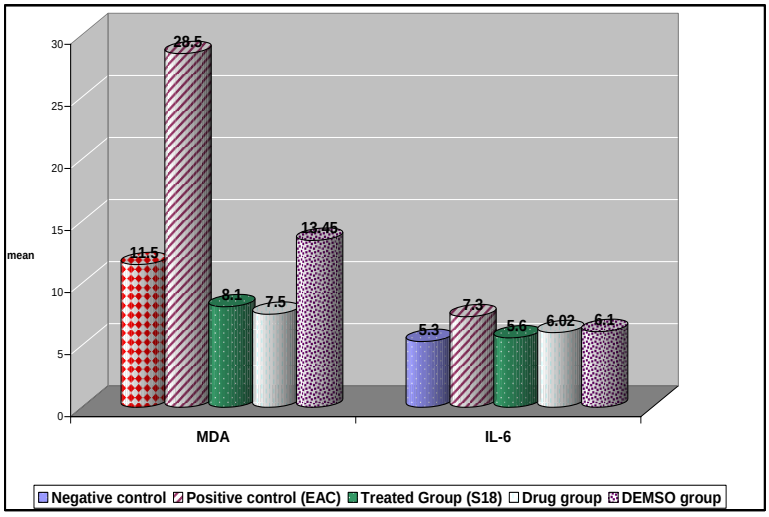

Fig. (5): Effect of Compound (S18) on MDA and IL-6 in all groups.

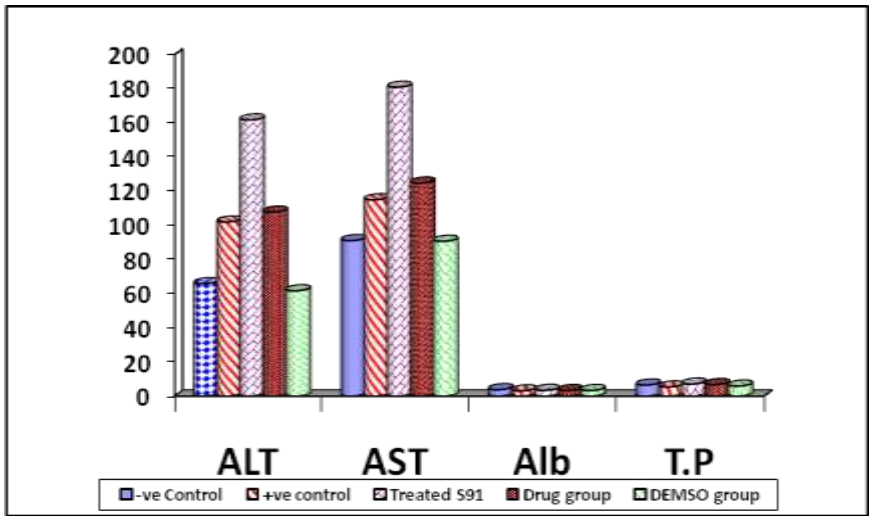

Fig. (6 a): Effect of Compound (S91) on liver functions in all groups.

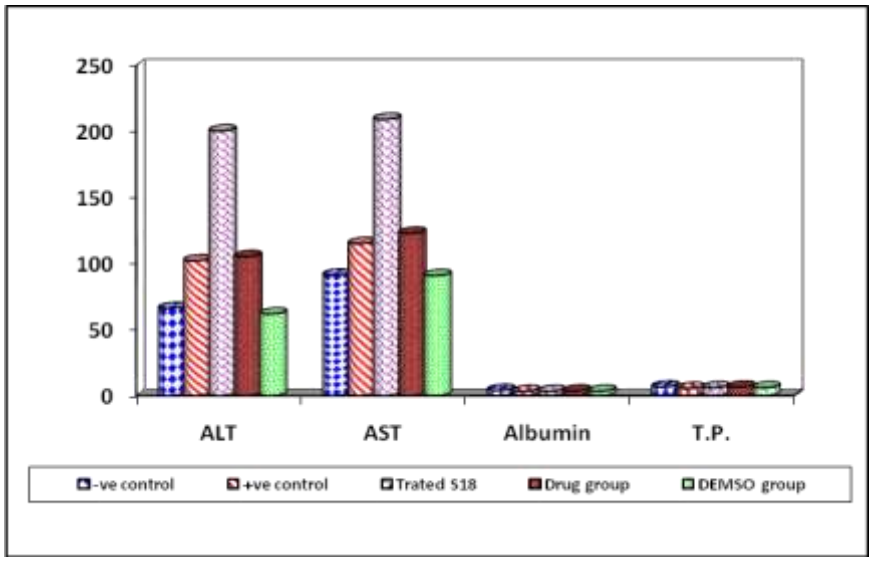

Figure (6 b): Effect of Compound (S18) on liver functions in all groups.

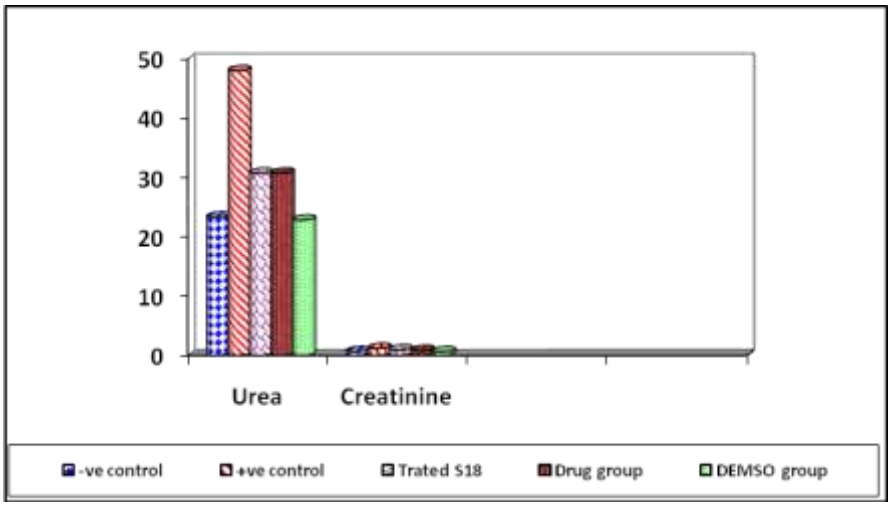

Figure (7 a): Effect of Compound (S91) on kidney functions in all groups.

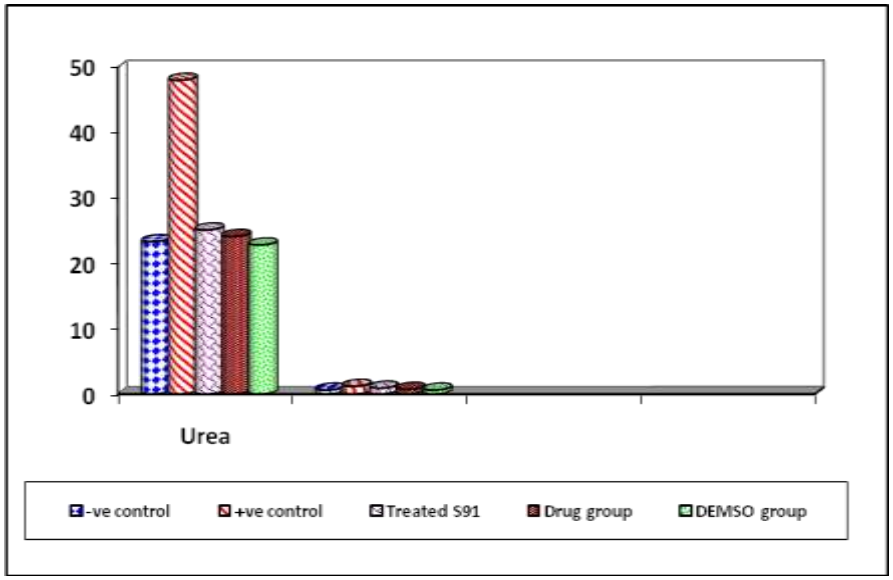

Figure (7 b): Effect of Compound (S18) on kidney functions in all groups.

Tables:

Table (I): Compound (S91) & (S18) effect on volume and count of tumor cells:

P	Treated Group (S18)	Treated Group (S91)	Positive Control Group	Variables
	Mean ± SD.	Mean ± SD.	Mean ± SD.	
0.001**	1.5 ±0.7	1.7 ±0.3	4.2 ±0.5	**Tumor Volume (ml)**
0.001**	112.6 ±58.1	14.1 ±2.9	216.4 ±34.5	**EAC cells Count ($\times 10^6$)**

Table (II): Compound (S91) & (S18) effect on anti-oxidants "SOD, GSH, Catalase" in EAC cells:

P	DEMSO group	Drug group	Treated Group (S91)		Positive control (EAC)		Negative control	Variables
	Mean ± SD	Mean ± SD	% Change	Mean ± SD.	% Change	Mean ± SD.	Mean ± SD.	
0.001**	13.45 ±1.9	15.9 ±1.7	66.66	9.5 ±1.3	147	28.5±4.9	11.5 ±2.1	**MDA**
0.001**	6.1 ±0.2	3.7 ±0.4	6.8	6.8 ±0.2	37.7	7.3 ±0.5	5.3 ±0.2	**IL-6**

Table (III): Effect of Compound (S91) on MDA and IL-6 in all groups:

P	Treated Group (S18)		Treated Group (S91)		Positive Control Group		Variables
	% Change	Mean ± SD.	% Change	Mean ± SD.	% Change	Mean ± SD.	
0.001**	80.1	131.9 ±17.1	275	274.5 ±23.8	-----	73.2 ±13.2	**SOD**
0.001**	77.2	16.3 ±12.2	206.5	28.2 ±2.5	-----	9.2 ±2.1	**GSH**
0.001**	900	0.5 ±0.01	360	0.23 ±0.1	------	0.05 ±0.01	**Catalase**

Table (IV): Effect of Compound (S18) on MDA and IL-6 in all groups:

P	DEMSO group	Drug group	Treated Group (S18)		Positive control (EAC)		Negative control	Variables
	Mean ± SD	Mean ± SD	% Change	Mean ± SD.	% Change	Mean ± SD.	Mean ± SD.	
0.001**	13.45 ±1.9	7.5 ±0.4	71.6	8.1 ±0.7	147	28.5±4.9	11.5 ±2.1	**MDA**
0.001**	6.1 ±0.2	6.02 ±0.1	30.4	5.6 ±0.2	37.7	7.3 ±0.5	5.3 ±0.2	**IL-6**

Table (V): Effects of Compound (S91) on liver function tests in all groups:

P	TP (g/dl)	ALB (g/dl)	AST (U/ml)	ALT (U/ml)	Group	
----	6.5±0.4	3.8±0.2	91.1±8.4	65.9±5.9	**Mean±SD**	**Negative control**
	------	-------	-----	-------	**%change**	
0.001*	5.4±0.8	3.1±0.7	115±9.2	102±8.3	**Mean±SD**	**Positive control (EAC)**
	16.9	18.4	26.23	54.77	**%change**	
0.001**	7.1 ±0.7	3.4 ±0.3	180.9 ±5.8	161.8 ±11.2	**Mean±SD**	**Treated Group (S91)**
	9.2	10.5	98.5	145.5	**%change**	
0.001*	6.8±0.6	3.3±0.3	124.8±4.3	107.8 ±5.1	**Mean±SD**	**Drug group**
	4.6	13.2	36.9	63.5	**%change**	
p>0.01	5.9±0.8	3.3±0.5	90.7±6.9	61.7±5.7	**Mean±SD**	**DEMSO group**
	9.2	13.2	0.4	6.3	**%change**	

Table (VI): Effects of Compound (S18) on liver function tests in all groups:

P	TP (g/dl)	ALB (g/dl)	AST (U/ml)	ALT (U/ml)	Group	
----	6.5±0.4	3.8±0.2	91.1±8.4	65.9±5.9	**Mean±SD**	**Negative control**
	------	-------	-----	-------	**%change**	
0.001*	5.4±0.8	3.1±0.7	115±9.2	102±8.3	**Mean±SD**	**Positive control (EAC)**
	16.9	18.4	26.23	54.77	**%change**	
0.001**	5.9±0.5	3.1±0.1	209.4 ±12.4	200.2 ±6.8	**Mean±SD**	**Treated Group (S18)**
	9.2	18.4	129.8	203.7	**%change**	
0.01*	6.4±0.5	3.4±0.3	122.7±11.9	105.1 ±6.5	**Mean±SD**	**Drug group**
	1.5	10.5	34.6	59.2	**%change**	
p>0.01	5.9±0.8	3.3±0.5	90.7±6.9	61.7±5.7	**Mean±SD**	**DEMSO group**
	9.2	13.2	0.4	6.3	**%change**	

Table (VII): Effects of Compound (S91) on kidneyfunction tests in all groups:

P	Creatinine (mg/dl)	Urea (mg/dl)	Group	
----	0.6±0.12	23.3 ±3.0	**Mean±SD**	**Negative control**
	-----	-----	**%change**	
0.001*	1.17±0.14	48±6.9	**Mean±SD**	**Positive control (EAC)**
	95	106	**%change**	
p>0.01	0.9 ±0.1	25.1 ±3.7	**Mean±SD**	**Treated Group (S91)**
	50	7.7	**%change**	
p>0.01	0.72±0.19	24.1 ±3.3	**Mean±SD**	**Drug group**
	16.6	3.4	**%change**	
p>0.01	0.6±0.13	22.8±1.7	**Mean±SD**	**DEMSO group**
	0	2.1	**%change**	

Table (VIII): Effects of Compound (S18) on kidneyfunction tests in all groups:

P	Creatinine (mg/dl)	Urea (mg/dl)	Group	
----	0.6±0.12	23.3 ±3.0	**Mean±SD**	**Negative control**
	-----	-----	**%change**	
0.001*	1.17±0.14	48±6.9	**Mean±SD**	**Positive control (EAC)**
	95	106	**%change**	
0.001**	0.9 ±0.1	30.7 ±17.7	**Mean±SD**	**Treated Group (S18)**
	50	31.7	**%change**	
0.001*	0.8±0.2	30.7 ±7.9	**Mean±SD**	**Drug group**
	33.3	31.7	**%change**	
p>0.01	0.6±0.13	22.8±1.7	**Mean±SD**	**DEMSO group**
	0	2.1	**%change**	

DISCUSSION:

The chemistry of heterocyclic compound continues to be an explore field in the organic or Pharmaceutical chemistry. The importance of triazole derivatives lies in the field that these have occupied a unique position in heterocyclic chemistry, due to its various biological activities[2]. Triazole is a unique template that is associated with several biological activities. More investigations must be carried out to evaluate more activities of triazole for many diseases whose treatment are difficult in the medical sciences. 1,2,46Triazolo[1,56a] pyridines constituted an important class of heterocyclic compounds, which are of considerable interest due to their uses as active ingredients in antihypertensive, bronchodilatory, antiinflammatory, analgesic and positive inotropic agents[25].

Considering that the chiral centers of triazole are located close to the 1, 2, 4-triazole ring, a key template in the binding their target sites, chirality is expected to play a crucial role in the bioactivities of triazoles[26]. Volume of EAC was significantly decreased by 59.5%, and by 64.3%, ($p<0.01$) in S91& S18 treated groups; respectively. Also, the mean count of EAC cells in the positive control group was found to be 126.52± 12.13 ($\times 10^6$), which significantly decreased by 34.7% and 47.9%, ($p<0.01$) in S91& S18 treated groups; respectively, compared to the positive control group, Fig. (2). S91 and S18 compound showed a significant increase in the life span prolongation to 25 days and 28 days by 78% and 100%; respectively compared to the positive control group.

It was considered as triazole derivatives act as free radical scavengers and antioxidants, inhibiting lipid peroxidation and oxidative DNA damage, with abilities to inhibit activation of NF-κB. Based on various experimental and theoretical results it

is definitely concluded that the phenolic (-OH) plays a major role in the activity of triazole derivatives[6]. The previous studies which have demonstrated that acetyl keto reversed the aging related increase in oxidative damage as it decreased lipid peroxidation and increased GSH in aged mice[27]. MDA levels showed a signifycant decreasein S91 and S18 treated groups by 66.6 %, ($p<0.01$) and by 71.6%; ($p<0.01$); respectively compared to the positive control group. The anticancer activity may be attributed to its ability to decrease the lipid peroxidation as mentioned by Debnath et al.,[28].

Anti-oxidant activity of S91 & S18 showed SOD activity, CAT activity and GSH levels was signifycantly increased in S91 and S18 treated groups by (275% and 80.1%, 360% and 900%, and 206.5% & 77.2%) ($p<0.001$) respectively; compared to the positive control group. Antioxidants may play an important role in preventing free radical damage associated with aging by interfering directly in the generation of radicals or by scavenging them. Glutathione changes the level of reactive oxygen species in isolated cells grown in a laboratory, which may reduce cancer development[29]. It was reported that during cancer growth, oxidative stress causes changes in glutathione redox state of different tissues thereby increasing glutathione disulfide (GSSG) levels inside cells and/or GSSG efflux from cells. This increase may be caused by an increase in peroxide production by tumor cells that can lead to GSH oxidation within the red blood cells and different tissues[30].

IL-6 levels were signifycantly decreased in S91 and S18 treated groups by 6.8% and 5.6% ($p<0.01$); respectively. One possibility is that the NF-κB transcription factor turns on transcription of the IL-6 gene. Anticancer drugs designed to block chromosome functioning may work much more effectively than targeted anticancer medicines that block the cytoplasmically located signaling pathways toward protein synthesis (cell growth)[7].

ALT & AST activity were highly significant increase in *S91*&*S18* by 145.3, 98%, and 203%, 129% ($p<0.001$); respectively; without significant difference in total protein and albumin levels compared to negative control group. As theses compounds results in liver injury causing elevation in secretion of liver enzymes without any effect on the synthetic capacity of hepatocytes. Although all these benefits, these compounds cause impairment of hepatocyte function will increase the activity/toxicity of low-clearance drugs that require metabolic detoxification by the liver[31]. Hepatotoxic reactions are among the most common, and potentially serious, adverse effects associated with triazole therapy. The mechanism of hepatotoxicity is classified typically according to liver function test results, although liver biopsy may be required to confirm the diagnosis. Reactions resulting in degeneration or necrosis of hepatocytes (hepatocellular injury) typically manifest with significant elevations (>3-fold) in serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) concentrations. Occasionally, triazole therapy may be associated with a mixed pattern of liver injury (hepatotoxic and cholestatic)[32].

These effects have not been shown to produce impaired renal functions, current labeling does not recommend the use of IV voriconazole (one of triazole derivatives) in patients

with moderate-to-severe renal impairment (i.e, estimated creatinine clearance (<50 mL/min), unless the benefit justifies the potential increased risk of toxicity[33].

CONCLUSION:

Finally, it could be concluded that our *in vivo* studies provide a support for the hypothesis the chiral centers of triazole are located close to the 1, 2, 4-triazole ring, a key template in the binding their target sites, chirality is expected to play a crucial role in the bioactivities of triazoles. Treatment of mice bearing tumor with triazole derivatives (S91 & S18) induced tumor growth regression and showed antioxidant activity by increasing the deteriorated levels of GSH and SOD in untreated groups and decreasing their elevated lipid peroxidation. But, they have hepatotoxicity affect the elevated levels of liver enzymes and no side effect on kidney function parameters.

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