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Protective Effect of Vitamin C on Acrylamide Induced Toxicity

Fayzah A. Aboubaker*.

Department of Zoology, College of Science, Sebha University. Libya.

ABSTRACT

Acrylamide is widely used and is formed during the various heating processes through the interaction of amino acids with carbohydrates, so it is a great danger to human and animal health. In this study, albino rats were divided into three groups; control rats, rats treated with acrylamide and rats treated with acrylamide and vitamin C. Results revealed that significant changes were observed in blood parameters where significant decrease in number of RBCs in rats drinking acrylamide there was increase the mean number of RBCs in rats drinking acrylamide and treated with vitamin C a decrease in hemoglobin contentand Hematocrit percent (HCT %) of mice treated with vitamin C, and an increase in mean white blood cell count in mice that drank acrylamide(9.30±3.88 10^3/µl)(7.69±2.65 10^3/µl), where a decrease was observed compared with those treated with vitamin C. For mice treated with vitamin C after a decrease in the acrylamide and lymphocyte group and a decrease in the mean number of neutrophils in the group treated by vitamin C. It was nice to point out the role that vitamin C plays as antioxidant nutrient as well as to describe the mechanisms that make them necessary for humans to acquire in diets. Further, we discuss the evidence for potentialbenefits consumed in amounts greater than required, for example as dietary supplements.

Aim of thestudy: This study was designed to elucidate the preventive and therapeutic role of vitamin C to avoid human exposure to acrylamide, which can come from several sources - especially the current diet- and find a way to reduce its toxic effect.

Keywords: Acrylamide, neurotoxicity, rats, vitamin C.

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Corresponding author

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INTRODUCTION

Acrylamide (AA) is a well-known neurotoxic, carcinogenic and genotoxic compound. It is used universally in the industrial process and recently found in various food products which are cooked at a temperature above 120˚C such as potato crisps, bread, cookies and French fries[1]. Acrylamide is a vinyl monomer having high water solubility.It is used in the manufacturing polyacrylamides, in cosmetic industries such as lotions, cosmetics, deodorants[2]. Recently, it was detected in certain food products which raises a worldwide concern because nowadays every individual exposed to AA contained food products such as coffee cookies, bread, potato crisps[3.4]. AA is produced when carbohydrate-rich foods are processed at high temperature (higher han120°C) during baking, grilling or frying[5]. It is carcinogenic, nephrotoxic, neurotoxic and induces reproductive toxicity exposure in mice and rats[6.7]. Children eat moreAA containing food than adults because they consume high AA rich diet and high calories relative to body weight [8].Dietary ACR is largely derived from heat-induced reactions (Maillard reaction) between the predominantly amino group of the free amino acid precursor asparagine and carbonyl groups of reducing sugar as glucose and fructose during heat processing of plant-derived foods such as potato fries and cereals. Orally consumed ACR is absorbed into the circulation then distributed to various organs, and reacts with DNA, neurons, hemoglobin, and essential enzymes [9].Vitamin C (ascorbic acid) is a required nutrient for a variety of biological functions. Humans and other primates have lost the ability to synthesize ascorbic acid due to a defect in L-gulono-1,4-lactone oxidase, an enzyme that catalyzes the conversion of L-gulonolactone into ascorbic acid. Humans, primates and a few other animals (e.g., guinea pigs) depend on the diet as a source of vitamin C to prevent the vitamin C deficiency disease, scurvy, and to maintain general health. The health-promoting effects of vitamin C can be attributed to its biological functions as a co-factor for a number of enzymes, most notably hydroxylases involved in collagen synthesis, and as a water-soluble antioxidant. Vitamin C can also function as a source of the signaling molecule, hydrogen peroxide[10.11]and in the treatment of cancer[12] and neurodegenerative diseases[13.14].

MATERIALS AND METHODS

Obtained Wester albino albino mice (male and female mice weighing about 80-120 g) from Animal House College of Science University Sebha. Animals were maintained on a standard diet and housed, in polystyrene cages in a room free from any source of chemical contamination, artificially light (12 h dark-light cycle) and thermally controlled (25 ± 2° C). All animals received human care according to the guidelines of the Ethics Committee. Experiments began after the animals were allowed to adapt for four weeks.

Rats were divided randomly into 5 groups as follows:G1: (control group): include 7 males and 7 females in separate cages were fed in normal diet.G2: (Acrylamide group): include 7 males and 7 females separately and were administered daily acrylamide in drinking water (50mg /kg body weight) for 4 weeks.G3: (Acrylamide and vitamin C group): include 7males and 7 females separately. Acrylamide was administered daily in drinking water as the above and vitamin C was given daily in drinking water for 4 weeks. Dissolved 5000mg of effervescent vitamin C tablets produced by the Chemical Industries DevelopmentCompany (CID) in 500 ml of water and each 1 ml of water contains 2 mg of vitamin C and given 20 ml of thesolution for the male cage and 30 ml for the female cage. After 4 weeks, from the beginning of theexperiment, rats of all group were sacrificed and blood sample were collected as follow: Rats were anesthetized with chloroform. Blood samples were collected directly form heart by 5ml syringe. Blood was collected inheparinized tubes from heart directly under deep an aesthesia with chloroform. Blood samples were divided into 2 parts, the first part for CBC, the second part for plasma preparation. Plasma was obtained from centrifugation of the 2nd part tubes for 10 min, 3000 r.p.m. Plasma was stored in -20˚ C until used.

At the end of the experimental period, rats were fasted overnight, anesthetized under diethyl ether, and then the rats from each group were sacrificed. The blood was collected and kept in tubes with and without anticoagulant for serum and plasma separation and for whole blood respectively. Serum and plasma samples were kept at -70 °C till analysis.

The results are expressed as Mean ±SE. Analysis of data was performed by one-way analysis of variance (ANOVA) followed by Post hock Duncan test using the SPSS v 25 (statistical package for social sciences) software for windows. P value less than 0.05 was considered statistically significant.

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RESULTS

External feature of acrylamide exposed rates morphologic changes were observed from the 4th week of acrylamide treatment. These changes are lossof weight and neuropathies, hands and feet numbness, gait abnormalities, muscle weakness, ataxia, skin damage in some case. The following studies were done.In the hematological study, the mean of hemoglobin content, WBCS, RBCS and platelets in rats drinking acrylamide and treated with vitamin C were evaluated.

The number of red blood cells (RBSs)

As shown in table 1, the mean number of RBCs (106/µl) in the control group was (6.42±0.57 x 10^6/µl) and in rats drinking acrylamide only the number was (5.82±0.70 x 10^6/µl) and the mean numbers of RBCs was (5.93±0.46 x 10^6/µl) in rats drinking acrylamide and treated with vitamin C. Statistically as show by one-wayANOVA test there was significant difference among all groups ($p < 0.05$) (figure 1). Student T-test showed that, there was significant decrease ($P < 0.05$) in number of RBCs in rats drinking acrylamide compared with control group (table 1).In addition, statistical analysis (t-test) indicated that, there was increase the mean number of RBCs in rats drinking acrylamide and treated with Vitamin C compared with acrylamide group with no significant difference; ($P > 0.05$). Moreover, there was increase the mean number of RBCs in rats drinking acrylamide and treated with vitamin C compared with control group with no significant difference; ($P > 0.05$) (table 1). On the other hand, there were no significant differences in RBCs (10^6/µl) between male and female in the three groups of the present study (table 2).

Hemoglobin (HB) content

As shown in table 1, the mean level of hemoglobin content (g/dl) in the control group was (12.00 ± 1.06 g/dl) and in rats drinking acrylamide only was (11.00±1.04 g/dl) while the level was (10.64±0.56 g/dl) in rats drinking acrylamide and treated with vitamin C. Statistically, one-way ANOVA test showed that, there was high significant difference among all groups ($p < 0.01$) (figure 2). Student T-test showed that, there was significant decrease ($P < 0.05$) in hemoglobin content in rats drinking acrylamide compared with control group.In addition, statistical analysis (t-test) indicated that there was a decrease in the Hemoglobin content (g/dl) in rats drinking acrylamide and treated with vitamin C compared with rats drinking acrylamide only with no significant difference ($P > 0.05$) and there was a decrease in the Hemoglobin content (g/dl) in rats drinking acrylamide and treated with vitamin C compared with control with high significant difference ($P < 0.001$)(table 1).

Also statistical analysis for the differences between male and female showed that there is no significant difference in hemoglobin content (g/dl) between male and female in the control group, and vitamin C group ($P > 0.05$). On the other hand, in acrylamide drinking rats, there was a highly significant decrease ($P < 0.01$) in hemoglobin content of male compared with female (table 2).

Hematocrit percent (HCT %)

As shown in table 1, the mean level of hematocrit percent (HCT %) in the control group was (31.42 ±1.98 %) and in rats drinking acrylamide only was (32.58±6.96 %) and the level was (31.38±2.06 %) in rats drinking acrylamide and treated with vitamin C. Statistically, one-way ANOVA test showed that there was no significant difference among all groups ($p > 0.05$) (figure 3). Student T-test showed that there was no significant difference ($P > 0.05$) in HCT in rats drinking acrylamide compared with control group.In addition, statistical analysis (t-test) indicated that, there was decrease of the HCT in rats drinking acrylamide and treated with vitamin C compared with rats drinking acrylamide only with no significant difference ($P > 0.05$) and also compared with control with no significant difference ($P > 0.05$) (table 1).Also statistical analysis for the differences between male and female showed that there is no significant difference in HCT between male and female in all groups ($P > 0.06$) (table 3).

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Table 1: RBCs and hemoglobin content in rats drinking Acrylamide and treated with Vitamin C

Groups		RBCs (10^6/µl)	Hemoglobin (g/dL)	HCT (%)
Control (G1)	Mean ± SD	6.42±0.57	12.00 ± 1.06	31.42 ±1.98
	Minimum	5.60	10.10	29.00
	Maximum	7.30	13.70	35.00
Acrylamide (G2)	Mean	5.82±0.70	11.00±1.04	32.58±6.96
	Minimum	4.60	8.40	12.20
	Maximum	6.90	12.30	38.00
Vitamin C (G3)	Mean ± SD	5.93±0.46	10.64±0.56	31.38±2.06
	Minimum	5.30	9.50	26.90
	Maximum	6.80	11.50	35.00
P value (ANOVA), P		< 0.05*	< 0.01*	> 0.05
Acrylamide vs Control (t-test) , P1		< 0.05*	< 0.05*	> 0.05
Vitamin C vs Control (t-test) , P1		< 0.05*	< 0.001**	> 0.05
Acrylamide vs Vitamin C (t-test) , P2		> 0.05	> 0.05	> 0.05

P: P value (one-way ANOVA), P1: Compared with control group; P2: Compared with acrylamide group.P > 0.05 considered not significant, *P < 0.05 considered significant, **P < 0.01 considered high significant, and ***P < 0.0001 considered extremely high significant.

Table 2: Statistical analysis of the mean number of RBSs and hemoglobin content in males and females of the different groups under study.

Group	RBCs (10^6/µl)			Hemoglobin(g/dL)		
	Mean ± SD		*P value*	Mean ± SD		*P value*
	Male	Female		Male	Female	
Control(n=12)	6.4 ±0.6	6.5±0.6	> 0.05	11.6±1.1	12.4±0.9	*> 0.05*
Acrylamide(n=14)	5.9±0.9	5.7±0.4	> 0.05	11.6±0.4	10.3±1.1	*< 0.01***
Vitamin C(n=14)	5.8±0.4	6.0±0.5	> 0.05	10.7±0.5	10.6±0.7	*> 0.05*

P: compared between male and female; P > 0.05 considered not significant, *P < 0.05 considered significant, **P < 0.01 considered high significant, and ***P < 0.0001 considered extremely significant.

Table 3: Statistical analysis of the mean of HCT in males and females of the different groups under study.

Group	Male	Female	P value
Control (n=12)	30.9±1.6	31.9±2.4	> 0.05
Acrylamide (n=14)	30.4±2.3	34.4±2.0	> 0.05
Vitamin C (n=14)	31.8±1.5	30.9±2.6	> 0.05

P > 0.05 considered not significant

The number of white blood cells (WBCs)

Table 4 indicates that the mean number of WBCs (10^3/µl) in control group was (7.16±1.94 10^3/µl) and in rats drinking acrylamide, the mean number was (9.30±3.88 10^3/µl) and also it was (7.69±2.65 10^3/µl) in rats drinking acrylamide and treated vitamin C. Statistically, one-way ANOVA test indicates that, there was no significant difference (p > 0.05) among three groups (figure 4). Student T-test indicates that, there was increase with no significant difference (P > 0.05) in number of WBCs (10^3/µl) in rats drinking acrylamide compared with control group (table 4). In addition, statistical analysis (t-test) indicates that, there was decrease the mean number of WBCs in rats drinking acrylamide and treated with vitamin C compared with rats

drinking acrylamide only with no significant difference (P > 0.05). In addition, statistical analysis (t-test) indicates that, there was increase the mean number of WBCs in rats drinking acrylamide and treated with vitamin C compared with control group with no significant difference (P > 0.05) (table 4).Statistical analysis (t-test) for the differences between males and females showed that, there was no significant difference (P > 0.05) in WBCsbetween males and females in the control group, and vitamin C group but in acrylamide drinking rats there was significant decrease (P < 0.05) in WBCs of male compared with female (table 5).

The mean number of platelets

As shown in table 4, the mean number of platelets (10^3/µl) in control group was (722.27±189.37 10^3/µl) and in rats drinking acrylamide, the number was (760.77±132.57 10^3/µl) moreover the number was (672.67±177.0910^3/µl), in rats drinking acrylamide and treated with vitamin C (figure 5). Statistical analysis, ANOVA test indicated that, there was no significant difference among the groups of the present study, (p > 0.05). Student T-test indicated that there was significant decrease (P > 0.05) in number of platelets (10^3/µl) in rats drinking acrylamide compared with control group (table 4).

In addition, statistical analysis (t-test) it indicates that, there was increase the mean number of platelets (10^3/µl) in rats drinking acrylamide treated with treated with vitamin C compared with rats drinking acrylamide only with no significant difference (P > 0.05). Also, statistical analysis (t-test) it indicates that, there was an increase in the mean number of platelets (10^3/µl) in rats drinking acrylamide treated with treated with vitamin C compared with control group with no significant difference (P > 0.05) (table 3).An extremely significant difference (P < 0.0001) in PLTs (10^3/µl) was observed between male and female in the control group; however, but there were no significant differences (P > 0.05) in the acrylamide group. On the other hand, in vitamin C group there was significant difference (P < 0.05) between male and female (table 5).

Table 4: WBCs and platelets in rats drinking acrylamide and treated with vitamin C.

Groups		WBCs (10^3/µl)	Pelts (10^3/µl)
Control (G1)	Mean ± SD	7.16±1.94	722.27±189.37
	Minimum	4.00	474
	Maximum	9.90	978
Acrylamide (G2)	Mean	9.30±3.88	760.77±132.57
	Minimum	4.3	500
	Maximum	16.1	1042
Vitamin C (G3)	Mean ± SD	7.69±2.65	672.67±177.09
	Minimum	4.5	483
	Maximum	13.9	1120
P value (ANOVA), P		> 0.05	> 0.05
Acrylamide vs Control (t-test) , P1		> 0.05	> 0.05
Vitamin C vs Control (t-test) , P1		> 0.05	> 0.05
Acrylamide vs Vitamin C (t-test) , P2		> 0.05	> 0.05

P: probability (one-way ANOVA); P1: compared with control group; P2: compared with acrylamide group; P > 0.05 considered not significant,

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Table 5: Statistical analysis of the mean of WBCs and PLTs content in males and females of the different groups under study.

Group	WBCs (10^3/µL)			PLTs (10^3/µl)		
	Mean ± SD		*P value*	Mean ± SD		*P value*
	Male	Female		Male	Female	
Control(n=12)	6.7±1.7	7.7±2.3	> 0.05	573.5±84.7	900.8±87.5	< 0.0001***
Acrylamide(n=14)	7.1±2.0	11.9±4.1	< 0.05*	739.7±69.3	785.3±187.3	> 0.05
Vitamin C (n=14)	8.3±3.4	7.1±1.7	> 0.05	559.7±86.7	785.7±175.6	*< 0.05* *

P: compared between male and female; P > 0.05 considered not significant
*P < 0.05 considered significant, **P < 0.01 considered high significant, and ***P < 0.0001 considered extremely significant.

The lymphocytes (%)

As shown in table 6, the mean number of Lymphocytes (%) in control group was (80.24±9.43 %) and in rats drinking acrylamide, the mean number was (80.56±8.72 %) and also it was (80.90±8.00 %) in rats drinking acrylamide and treated vitamin C. Statistically, one-way ANOVA test indicates that there was no significant difference (p > 0.05) among three groups (figure 6). Student T-test indicates that there was an increase with nosignificant difference (P > 0.05) in number of lymphocytes in rats drinking acrylamide compared with control group (table 6). In addition, statistical analysis (t-test) indicates that, there was increase the mean of Lymphocytes in rats drinking acrylamide and treated with vitamin C compared with rats drinking acrylamide only with no significant difference (P > 0.05) (table 6). In addition, statistical analysis (t-test) indicates that, there was an increase in the mean number of lymphocytes in rats drinking acrylamide and treated with vitamin C compared with control group with no significant difference (P > 0.05) (table 6).Statistical analysis (t-test) for the differences between males and females showed that there was significant difference (P < 0.05) in lymphocytes between males and females in the control group and acrylamide group but in vitamin C group there was no significant difference (P > 0.05) in lymphocytes of male compared with female (table 7).

Neutrophils (%)

As table 6 indicates, the mean number of neutrophils (%) in control group was (11.78±7.38 %) and in rats drinking acrylamide, the number was (10.63±7.02 %) moreover the number was (10.73±5.85 %), in rats drinking acrylamide and treated with vitamin C (figure 7). Statistical analysis, ANOVA test indicated that there was no significant difference among the groups of the present study, (p > 0.05). Student T-test indicated that, there was significant decrease (P > 0.05) in number of neutrophils in rats drinking acrylamide compared with control group (table 6). In addition, statistical analysis (t-test) it indicates that there was a decrease the mean of neutrophils in rats drinking acrylamide treated with vitamin C compared with rats drinking acrylamide only with no significant difference (P > 0.05) (table 5). Also, statistical analysis (t-test) indicates that there was an increase in the mean number of Neutrophils in rats drinking acrylamide treated with treated with vitamin C compared with control group with no significant difference (P > 0.05) (table 6).Statistical analysis (t- test) for the differences between males and females showed that there was high significant difference (P < 0.01) in neutrophils between males and females in the control group and acrylamide group but in vitamin C group there was no significant difference (P > 0.05) in neutrophils of male compared with female (table 7).

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Table 6: Lymphocyte (%) and neutrophils (%) in rats drinking acrylamide and treated with vitamin C.

Groups		WBCs (10^3/µl)	Pelts (10^3/µl)
Control (G1)	Mean ± SD	80.24±9.43	11.78±7.38
	Minimum	59.20	5.40
	Maximum	88.70	26.90
Acrylamide (G2)	Mean	80.56±8.72	10.63±7.02
	Minimum	60.30	2.80
	Maximum	91.50	28.70
Vitamin C (G3)	Mean ± SD	80.90±8.00	10.73±5.85
	Minimum	56.60	6.30
	Maximum	87.60	28.70
P value (ANOVA), P		> 0.05	> 0.05
Acrylamide vs Control (t-test) , P1		> 0.05	> 0.05
Vitamin C vs Control (t-test) , P1		> 0.05	> 0.05
Acrylamide vs Vitamin C (t-test) , P2		> 0.05	> 0.05

P: probability (one-way ANOVA); P1: compared with control group; P2: compared with acrylamide group; P > 0.05 considered not significant,

Table 7: Statistical analysis of the mean of lymphocyte neutrophils in males and females of the different groups under study

Group	WBCs (10^3/µL)			PLTs (10^3/µl)		
	Mean ± SD		*P value*	Mean ± SD		*P value*
	Male	Female		Male	Female	
Control (n=12)	74.5±10.7	85.9±2.3	< 0.05*	17.2±6.9	6.4±1.3	< 0.01*
Acrylamide (n=14)	74.3±9.3	85.8±3.4	< 0.05*	15.7±7.7	6.4±2.2	< 0.01*
Vitamin C (n=14)	82.8±2.6	79.0±3.2	> 0.05	9.0±1.4	12.5±3.1	> 0.05

P: compared between male and female; P > 0.05 considered not significant
*P < 0.05 considered significant, **P < 0.01 considered high significant, and ***P < 0.0001 considered extremely significant.

DISCUSSION

Mechanism of acrylamide toxicity:

Acrylamide have significant binding capacity to liver, kidney, brain and erythrocyte [15]. Nowadays, the presence of acrylamide in lots of fried and baked foods raises concerns due to its potential to cause toxicity and cancer in animals and human. Consequently, a number of papers have focused on evaluation of various chemicals in reduction of acrylamide in various antioxidants as well as decreasing its related toxicities . In addition, plants are important sources of diverse metabolites antioxidants demonstrating possible effectiveness in acrylamide toxicity or reduction of acrylamide content in food sources [16]. Several mechanisms have explained how acrylamide induce its toxic effect. Acrylamide contains α,-unsaturated amide system that reacts with nucleophilic compounds via Michael addition. The majorsiteofreactionissulfhydrylgroupscontainedonproteinsandaminoacids. Onceabsorbed, acrylamide may be conjugated by glutathione-S-transferase (GST) t o N -acetyl-S-(3-amino-3-oxopropyl) cysteine or it reacts with cytochrome P450 (CYP450)to produce glycidamide, which is more reactive toward DNAandproteinsthantheparentcompound,acrylamide[17],orformingaDNAreactiveepoxide[18] [19].Oxidative stress is considered as one of the important mechanisms of toxic effects of acrylamide. ACR causes oxidative damage through inducing the generation of reactive oxygen species(ROS) which enhanced the production of lipidperoxidase reducing the antioxidant defence systems[20].Liver, kidney, brain and erythrocyte GST

have significant binding capacity with acrylamide, being higher with the liver[21].This study is consistent with the results of both Elgarawany *et al*., 2019and Shrivastava*et al*., 2019[22.1].

Immunomodulatory efficacy

Results shown in Hematological study reveal the effect of administration of vitamin C on immune functions, it was clear that, vitamin C elicited significant increase of immunomodulatory efficacy in when compared with acrylamide intoxicated rats, while acrylamide significantly decrease them in comparison with control group. On the other hand, administration of vitamin C could be attributed to the antioxidant activity of vitaminC. These results agree with Ivanov, 2008 [23] who stated that there is a lot of information about the role of free radicals in the immune defence mechanism (IgG, IgM) where the involvement of free radicals leading to weakness of immunity. Also, these findings were coincided with others who concluded that the supplementation with the antioxidant protected immune responses in individuals exposed to certain environmental sources of free radicals [24]. Many of the protective functions of immune cells depend on the fluidity of the membranes of the cell. As the concentration of polyunsaturated fatty acids in the membranes is increased, the potential for membrane lipid peroxidation mediated by free radicals also is increased. Lipid peroxidation decreases membrane fluidity which adversely affects immune responses. Mice fed oxidized lipids show marked atrophy of the thymus and T-cell dysfunction. Loss of membrane fluidity has been related directly to the decreased ability of lymphocytes to respond to challenges to the immune system [25].

Clinical Signs

Both acrylamide and glycidamide have a significant affinity for binding to plasma proteins, in particular, to Hb[26]. Tarskikh (2006) observed some changes in physiochemical characteristics of biological membranes, decrease in erythrocyte acid resistance and activation of LPO at the early stage after ACR administration accompanied by a decrease in erythrocyte count[27]. The present study revealed that Hb decreased significantly after oral administration of ACR as reported by Ivanov, 2008 [23]. in which the ACR covalently binds to the cysteine residues and forms adducts with sulfhydryl groups on hemoglobin, resulting in the loss of heme part of hemoglobin molecules, hereby reducing the amount of Hb in the blood, which in turn may also be responsible for the anemic conditions as evident by the low level of RBCs observed in the present investigation [29]. The present study also showed significant change in the total white blood cell count (WBCs) following ACR treatment. This change in total WBCs count suggests that ACR may be immunosuppressive. This change could be due to their diminished production, redistribution from peripheral blood into the tissues or rapid destruction of WBCs [30].

CONCLUSION

Acrylamide caused many adverse effects in the tissues and hematological standards reflected in significantincrease that caused damage to them. The administration of vitaminC in combination with acrylamide significantly improves blood disorders as well as improves immunestatus reflected in increased Ig G and Ig M.

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