

## Biochemical and Hematological Effects of Food Flavoring Furfural in Male Albino Rats

Tarek M. Ali<sup>1\*</sup>, Osama M. Ahmed<sup>2</sup>, Rasha R. Ahmed<sup>3</sup>.

<sup>1</sup> Physiology Department, Faculty of Medicine, <sup>2</sup> Physiology Division, and <sup>3</sup> Histology division, Zoology Department, Faculty of Science, Beni-Suef University

### ABSTRACT

**Objectives:** The present study aims to assess the effect of furfural, an aldehyde commonly used as food flavor in many foods, on the hematological and biochemical aspects in male albino rat. **Materials and methods:** The experimental animals used in the study were divided into four groups. The control group was given a daily volume of the vehicle dimethyl sulfoxide (DMSO) whereas the other three groups were orally administered furfural for 8 weeks in a dose of 3.18, 6.36 and 12.72 mg/kg body weight respectively. Blood samples were obtained for complete blood count (CBC), liver and kidney function tests. Serum  $\alpha$ -fetoprotein (AFP) and carbohydrate antigen (CA<sub>19,9</sub>) were also measured. **Results:** Obtained results revealed a decrease in red blood corpuscles (RBCs) count, packed cell volume (PCV) and hemoglobin content and an increase in mean cell volume (MCV) and mean cell hemoglobin content (MCH) in rats received furfural in a dose dependent manner. The white blood cells (WBC) count was decreased specially eosinophils percentage was depleted in the low and medium doses groups. Furfural elevated serum liver enzymes activities and total bilirubin concentration. The serum total proteins and albumin levels were increased in medium and high doses groups, while globulin level, was elevated only in low dose group. Furfural elevated serum urea level but did not affect serum AFP and CA<sub>19,9</sub> levels in all groups. **Conclusions:** In conclusion, furfural administration to rats induces a sort of macrocytic anemia, leucopenia, eosinopenia and elevated liver enzymes and urea in rats in a dose related manner.

### INTRODUCTION

Furfural (furan-2-carboxy-aldehyde, C<sub>4</sub>H<sub>3</sub>OCHO) was first extracted in 1840 through the bran distillation (Latin: furfur) by diluted sulfuric acid<sup>(1)</sup>. Furfural is a colorless liquid with pleasant aroma and it is partially soluble in water. It has a significant use as a selective solvent of mineral oil products, in chemistry, in the rubber industry, plastic surgery

and polymer industry<sup>(2)</sup>. It is also present in orange juice, brandy<sup>(3)</sup> and Japanese sake<sup>(4)</sup>. In the organism, furfural occurs by pentose dehydration<sup>(5)</sup>. In Europe, furfural is used as a flavor in foods such as baked goods, frozen dairies, meat products, candy, puddings, beverages, and gravies<sup>(6)</sup>. Furfural is a carcinogen classified in EU as a Category 3 carcinogen. In mice, it increased the incidence of hepatocellular adenomas

and carcinomas in males and of hepatocellular adenomas and fore stomach papillomas in females<sup>(7)</sup>. Furfural is eliminated slowly and in unchanged form through the kidneys and lungs. The liver oxidizes it into pyromucic acid ( $C_4H_3O_3COOH$ ) which is toxic to hepatocytes, but it is conjugated with glycine and mostly excreted in urine<sup>(8,9)</sup>. Furfural is unsaturated cyclic aldehyde, it is a known hepatotoxic substance<sup>(10)</sup>, and it changes the activity of some enzymes in the liver in acute<sup>(11)</sup> and chronic<sup>(12)</sup> experiments. Furfural may cause morphologic changes in the liver<sup>(13)</sup> that in the acute experiment are manifested in diffuse necrosis associated with regeneration of hepatocytes and terminate within a few days with liver recovery. It is presumed that liver damage is induced by oxidation of furfural. In the chronic experiment, furfural induces cirrhotic changes<sup>(13)</sup> associated with pseudobule formation, enlargement of the portal area, and destruction of the border plaque. In the liver parenchyma, a marked bridging necrosis and hydropic degeneration of hepatocytes develop. Simultaneously, various degrees of liver insufficiency may become evident<sup>(14,15)</sup>. Liver transaminases, AST and ALT are important markers of liver damage and are routinely done in modern laboratories. Also,  $\gamma$ -GT and alkaline phosphatase (ALP) are increased in cases where there is damage to liver parenchyma under the influence of many harmful substances which are detoxified in the liver every day<sup>(16)</sup>.

The aim of the current study is to clarify the hazards of oral furfural use in different doses on the

hematological and biochemical parameters including liver and kidney functions tests in male albino rats

## MATERIALS & METHODS

### Experimental animals:

Male albino rats (*Rattus norvegicus*) weighing 140-160 g were obtained from the animal house of Institute of Ophthalmology, Giza, Egypt. They were housed in plastic cages with good aerated covers at normal temperature and normal daily light-dark cycle. The animals were fed standard diet pellets and tap water *ad libitum*. They were kept under observation for 2 weeks to exclude any intercurrent infection and for proper acclimatization. All animal procedures were in accordance with the recommendations for the proper care and use of laboratory animals of Canadian Council on Animal Care (CCAC)<sup>(17)</sup>.

### Furfural:

2-Furancaboxyaldehyde, known commercially as furfural, was obtained from Aldrich company, Gillingham, England. The different doses of furfural-dissolved in dimethyl sulfoxide (DMSO)-were given daily to rats by gastric intubation between 8-10 AM. Three doses were chosen on the basis of the oral LD50 value which was previously determined by Jenner et al.<sup>(18)</sup> and equals 127 mg / Kg body weight.

### Animal Grouping and Experimental design:

The experimental animals used in the present study were divided into four groups. One group was kept as control and was given a daily

respective volume of the vehicle (DMSO) whereas the other three groups were orally administered 1/40, 1/20 and 1/10 of LD50 corresponding to approximately to 3.18, 6.36 and 12.72 mg/kg body weight respectively.

All groups were treated for 8 weeks. At the end of that period, rats were sacrificed and blood samples were obtained from jugular vein in two tubes, one containing ethylene diamine tetraacetic acid solution 15% (50 µl EDTA/5 ml blood) for determination of blood indices and the other without EDTA. After blood coagulation in the 2<sup>nd</sup> tube, blood was centrifuged at 3000 rpm for 15 minutes. Serum was obtained from each tube and kept at -30°C till used for biochemical determination.

#### **Hematological Examination:**

Counting of the red blood corpuscles (RBCs) and white blood cells (WBCs) was carried out by Neubauer slide, using saline (0.9 % NaCl)<sup>(19)</sup> and Turk's fluid<sup>(20)</sup> respectively. The hematocrit value was determined according to **Dacie and Lewis**<sup>(21)</sup> and the hemoglobin content was measured as described by **Lucky**<sup>(22)</sup>. Also, mean cell volume (MCV), mean cell hemoglobin content, and mean cell hemoglobin concentration percent (MCHC) were calculated according to **Dacie and Lewis**<sup>(21)</sup>. Blood film was prepared, fixed in methanol and then stained with Giemsa stain according to the methods of **Houwen**<sup>(23)</sup>.

#### **Biochemical Examinations:**

Serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activities were determined according to the method of

**Bergmeyer et al.**<sup>(24)</sup>, respectively, using reagent kits purchased from Spinreact company (Spain). Serum gamma-glutamyl transferase (γ-GT) activity was determined according to **Beleta and Gella**<sup>(25)</sup>. Serum alkaline phosphatase (AP) activity was assayed according to the method of **Belfield and Goldberg**<sup>(26)</sup> using reagent kit obtained from BioMerieux Chemical company (France). Serum lactate dehydrogenase activity was estimated by kits obtained from Stanbio Laboratories (USA) according to the method of **Bühl and Jackson**<sup>(27)</sup>. Total bilirubin concentration was determined according to the method of **Jendrassik and Grap**<sup>(28)</sup> using reagent kits purchased from Diamond Diagnostics Chemical Company, Egypt.

Serum total protein and serum albumin levels were estimated according to **Henry**<sup>(29)</sup> and **Doumas et al.**<sup>(30)</sup> using reagent kits purchased from Diamond Diagnostics Chemical company, Egypt. Serum globulin level was calculated by subtracting albumin level from total protein concentration. In addition, the ratio of albumin to globulin was calculated.

Serum α-fetoprotein (AFP) concentration was determined by a radioimmunoassay kit [Double antibody kit, Diagnostic Products Corporation (DPC), USA] according to the methods of **Waldmann and McIntire**<sup>(31)</sup> and **Wepsic**<sup>(32)</sup>. Serum carbohydrate antigen (CA<sub>19,9</sub>) was estimated by an immunoradiometric assay kit (Coat-A-Count GI-MA IRMA, DPC, USA) according to the method of **Ferbourg et al.**<sup>(33)</sup>. Both AFP and CA<sub>19,9</sub> concentrations were measured in the Radioactive Isotope

Unit, National Research Center, Dokki, Cairo, Egypt.

Serum urea and creatinine concentrations were measured based respectively on the methods of **Patton and Crouch**<sup>(34)</sup> and **Henry**<sup>(35)</sup> using reagent kits produced by Diamond Diagnostics (Egypt). Serum uric acid level was determined according to the method of **Barham and Trinder**<sup>(36)</sup> using reagent kits obtained from Spinreact Company (Spain).

**Statistical analysis:** The data were analyzed using the one way analysis of variance (ANOVA)<sup>(37)</sup> followed by LSD analysis to compare various groups with each other. Results were expressed as mean  $\pm$  standard error (SE). Values of  $P > 0.05$  were considered statistically non-significantly different, while values of  $P < 0.05$  and  $P < 0.01$  were significantly and highly significantly different respectively. F-probability expresses the general effect between groups.

## RESULTS

### Hematological effects:

The administration of furfural to albino rats for 8 weeks produced significant decrease of red blood corpuscles count, hematocrit (PCV) and hemoglobin content at the medium and high doses (6.36 and 12.72 mg/kg body weight) in a dose dependent manner. However, these parameters were not significantly affected at low dose (3.18 mg/kg body weight). In contrast, mean cell volume (MCV) of red blood corpuscles as well as mean cell hemoglobin (MCH) were highly significantly ( $P < 0.01$ ; LSD) increased as a result of

administration of medium and high concentration of furfural in a dose dependent manner. Mean cell hemoglobin concentration (MCHC) was not significantly ( $P > 0.01$ ; LSD) affected as a result of all tested doses of furfural. ANOVA results revealed that the effect between groups on RBC count, MCH and MCV was very highly significant ( $P < 0.001$ ; F-prob.) while the effect on hematocrit, Hb and MCHC was only significant ( $P < 0.05$ ; F-prob.) (Table1).

The white blood cells (WBC) or leucocytes count was significantly decreased due to furfural administration for 8 weeks; the percentage decreases were 26.804, 41.842 and 40.689 % respectively as a result of low, medium and high doses of furfural. Both lymphocytes and monocytes percentages were detectably decreased in furfural-administered animals although these changes were not significant. Eosinophils percentage was highly significantly depleted as a result of low and medium doses administration. Basophils percentage was also not significantly affected. ANOVA results revealed that while the effect between groups on WBC count and neutrophil percent was highly significant ( $P < 0.01$ ; F-prob.), the effect on eosinophil percent was very highly significant ( $P < 0.001$ ; F-prob.) (Table2).

### Biochemical Effects:

Serum ALT, AST,  $\gamma$ GT, ALP and LDH activities as well as total bilirubin concentration were remarkably increased as a result of furfural administration. The LDH activity and total bilirubin concentration were increased in a dose

dependent manner. While the low dose produced the most potent effect on AST activity, the high dose seemed to be the most effective on ALT,  $\gamma$ GT, ALP and LDH activities and total bilirubin concentration. One-way ANOVA indicated that the general effect was significant ( $P < 0.05$ ; F-prob.) on LDH activity, highly significant ( $P < 0.01$ ) on  $\gamma$ GT activity and total bilirubin concentration and very highly significant ( $P < 0.001$ ) on ALT, AST and ALP activities (Table 3).

The serum total protein and albumin levels were significantly ( $P < 0.05$ ; LSD) and highly significantly ( $P < 0.01$ ; LSD) increased as a result of medium and high doses of furfural, respectively (figure 1). Serum globulin level, on the other hand, was significantly elevated due only to low dose. A/G ratio was

significantly ( $P < 0.01$ ; LSD) increased as a result of low and high dose of furfural (figure 2). Serum AFP and CA<sub>19.9</sub> levels was non-significantly affected as a result of all tested doses of furfural (figure 3) as indicated by one-way ANOVA (highly significantly ( $P < 0.01$ ; F-prob.) and LSD test ( $P > 0.05$ )).

Serum creatinine and uric acid levels were not significantly changed in furfural administered rats. Serum urea level, on the other hand, was highly significantly increased as a result of all tested doses of furfural; the percentage increases were 32.665, 56.903 and 42.820 respectively due to low, medium and high doses respectively (Table 4). One-way ANOVA revealed that the effect between groups on urea level and A/G ratio was highly significant and significant respectively.

Table 1: The effect of furfural on hematological indices of rats in control , low ,moderate and high dose groups

Group	Parameter	Total RBCs count x 10 <sup>6</sup> /μl	%	PCV %	%	Hb (g/dl)	%	MCH Pg	%	MCV (fl (μ <sup>3</sup> ))	%	MCHC %	%
	<b>Control</b>		5.732 ± 0.122 <sup>a</sup>		46.481 ± 0.229 <sup>a</sup>		13.549 ± 0.292 <sup>a</sup>		23.549 ± 0.845 <sup>c</sup>		81.430 ± 1.842 <sup>c</sup>		29.287 ± 1.031 <sup>a</sup>
<b>Furfural treated</b>	<b>Low dose</b>	6.036 ± 0.497 <sup>a</sup>	+ 5.303	45.130 ± 0.594 <sup>ab</sup>	- 2.906	12.169 ± 0.384 <sup>b</sup>	- 2.804	20.902 ± 1.898 <sup>c</sup>	- 11.847	82.311 ± 7.252 <sup>bc</sup>	+ 1.082	27.224 ± 1.074 <sup>a</sup>	- 7.044
	<b>Moderate dose</b>	4.641 ± 0.282 <sup>b</sup>	- 21.528	43.604 ± 1.806 <sup>bc</sup>	- 6.189	12.587 ± 0.289 <sup>ab</sup>	- 7.100	28.310 ± 1.149 <sup>b</sup>	+ 19.396	98.635 ± 6.727 <sup>b</sup>	+ 21.128	28.958 ± 1.368 <sup>a</sup>	- 1.123
	<b>high dose</b>	2.702 ± 0.141 <sup>c</sup>	- 52.861	41.574 ± 0.123 <sup>c</sup>	- 10.557	11.692 ± 0.694 <sup>b</sup>	- 13.705	43.837 ± 1.695 <sup>a</sup>	+ 84.880	156.611 ± 4.887 <sup>a</sup>	+ 92.320	28.176 ± 1.435 <sup>a</sup>	- 3.793
<b>F-probability</b>		P < 0.01		P < 0.05		P < 0.05		P < 0.001		P < 0.001		P > 0.05	
<b>LSD at 5%</b>		0.887		2.831		1.318		4.303		16.500		-	
<b>LSD at 1%</b>		1.210		3.861		1.798		5.869		22.503		-	

- Data are expressed as Mean ± SE. Number of animals in each group is six.

- Means, which share the same superscript symbol(s), are not significantly different.

Table 2: The effect of furfural on total and differential WBCs count ( % of total ) in control , low ,moderate and high dose groups

Parameter Group	Total WBCs count x 10 <sup>3</sup> /μl	%	Differential WBCs count ( % o total )										
			Lympho cytes	%	Neutrophil (segmented)	%	Mono cytes	%	Eosinophil	%	Baso phil	%	
Control	7.980 ± 1.009 <sup>a</sup>		75.5 ± 2.473 <sup>a</sup>		17.333 ± 1.202 <sup>c</sup>		1.666 ± 0.333 <sup>a</sup>		7.000 ± 0.683 <sup>a</sup>		0		
Furfural treated	Low dose	5.841 ± 0.578 <sup>b</sup>	- 24.804	70.00 ± 5.360 <sup>a</sup>	- 7.285	26.000 ± 1.341 <sup>a</sup>	+ 50.003	0.833 ± 0.477 <sup>a</sup>	- 50	3.000 ± 0.730 <sup>b</sup>	- 57.143	0	
	Moderate dose	4.641 ± 0.393 <sup>b</sup>	- 41.842	74.833 ± 2.856 <sup>a</sup>	- 0.883	21.166 ± 1.351 <sup>bc</sup>	+ 22.113	1.000 ± 0.258 <sup>a</sup>	- 39.975	3.666 ± 0.333 <sup>a</sup>	- 47.628	0	
	high dose	4.733 ± 0.553 <sup>b</sup>	- 40.689	69.333 ± 4.402 <sup>a</sup>	- 8.168	22.000 ± 5.190 <sup>ab</sup>	+ 26.925	0.500 ± 0.498 <sup>a</sup>	- 69.988	8.000 ± 0.806 <sup>a</sup>	+ 14.286	0	
F-probability	P < 0.01		P > 0.05		P < 0.01		P > 0.05		P < 0.001		P > 0.05		
LSD at 5%	1.986		-		4.634		-		1.957		-		
LSD at 1%	2.708		-		6.321		-		2.669		-		

- Data are expressed as Mean ± SE. Number of animals in each group is six.
- Means, which share the same superscript symbol(s), are not significantly different.
- Stuff cells are zero in all groups

Table 3: The effect of furfural on liver enzymes and total bilirubin in control , low ,moderate and high dose groups

Parameter Group		ALT (U/L)	%	AST (U/L)	%	$\gamma$ GT (U/L)	%	ALP (U/L)	%	LDH (U/dl)	%	Total bilirubin (mg/dl)	%
Control		41.300 $\pm$ 3.309 <sup>b</sup>		154.00 $\pm$ 3.443 <sup>c</sup>		15.333 $\pm$ 0.882 <sup>c</sup>		203.100 $\pm$ 1.050 <sup>b</sup>		90.383 $\pm$ 8.490 <sup>b</sup>		0.566 $\pm$ 0.042 <sup>b<sup>a</sup></sup>	
Furfural treated	Low dose	64.681 $\pm$ 4.246 <sup>a</sup>	+ 5.303	248.600 $\pm$ 20.907 <sup>a</sup>	+56.612	19.600 $\pm$ 0.219 <sup>b</sup>	+27.829	332.000 $\pm$ 7.399 <sup>a</sup>	+ 63.466	93.906 $\pm$ 6.389 <sup>b</sup>	+ 3.898	0.675 $\pm$ 0.054 <sup>b</sup>	+ 19.257
	Moderate dose	63.375 $\pm$ 2.897 <sup>a</sup>	+ 53.450	207.400 $\pm$ 7.779 <sup>b</sup>	+34.675	19.012 $\pm$ 1.258 <sup>bc</sup>	+23.994	329.066 $\pm$ 11.078 <sup>a</sup>	+62.071	100.150 $\pm$ 0.980 <sup>b</sup>	+10.806	0.883 $\pm$ 0.079 <sup>a</sup>	+56.007
	high dose	66.425 $\pm$ 5.571 <sup>a</sup>	+60.835	201.400 $\pm$ 3.443 <sup>b</sup>	+30.773	24.050 $\pm$ 2.393 <sup>a</sup>	+56.851	388.366 $\pm$ 37.933 <sup>a</sup>	+88.757	117.566 $\pm$ 3.692 <sup>a</sup>	+30.075	0.921 $\pm$ 0.069 <sup>a</sup>	+62.721
F-probability		P < 0.001		P < 0.001		P < 0.01		P < 0.0001		P < 0.05		P < 0.01	
LSD at 5%		12.200		33.679		4.206		59.323		16.655		0.185	
LSD at 1%		16.639		45.933		5.737		80.908		22.715		0.252	

- Data are expressed as Mean  $\pm$  SE. Number of animals in each group is six.
- Means, which share the same superscript symbol(s), are not significantly different.

Table 4: The effect of furfural on some kidney functions tests in control , low ,moderate and high dose groups

Parameter		Uric acid (mg/dl)	%	Creatinine (mg/dl)	%	Urea (mg/dl)	%
Group							
Control		3.100 ± 0.150 <sup>a</sup>		1.091 ± 0.059 <sup>a</sup>		36.583 ± 3.429 <sup>b</sup>	
Furfural treated	low dose	3.550 ± 0.117 <sup>a</sup>	+ 14.516	1.100 ± 0.031 <sup>a</sup>	+ 0.917	48.533 ± 2.890 <sup>a</sup>	+ 32.665
	Moderate dose	2.966 ± 0.088 <sup>a</sup>	- 4.322	1.183 ± 0.134 <sup>a</sup>	+ 8.432	57.400 ± 2.818 <sup>a</sup>	+ 56.903
	high dose	3.000 ± 0.223 <sup>a</sup>	- 3.225	1.125 ± 0.104 <sup>a</sup>	+ 3.116	52.250 ± 2.219 <sup>a</sup>	+ 42.820
F-probability		P > 0.05		P > 0.05		P < 0.01	
LSD at 5%		-		-		8.472	
LSD at 1%		-		-		11.554	

- Data are expressed as Mean ± SE. Number of animals in each group is six.
- Means, which share the same superscript symbol(s), are not significantly different.

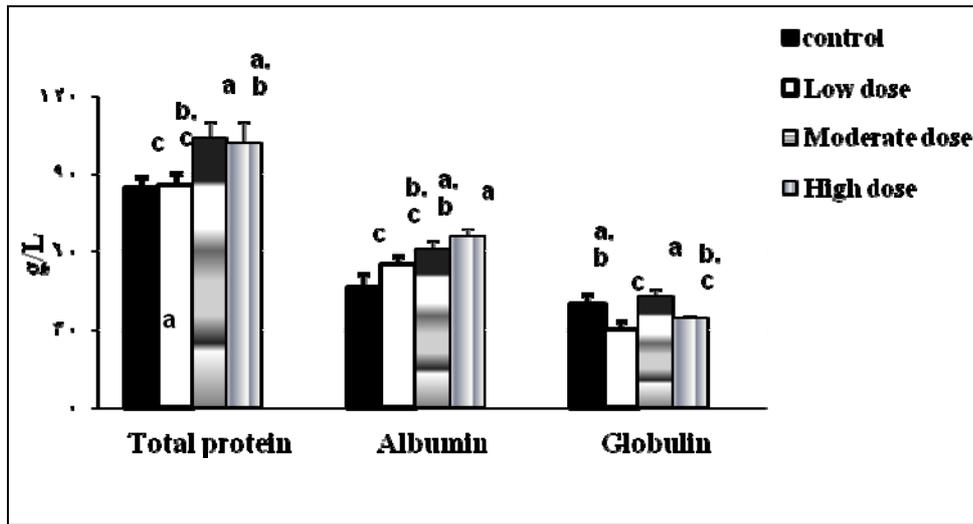


Figure 1: The effect of furfural on plasma protein levels in control, low, moderate and high dose groups. Means, which share the same superscript symbol(s), are not significantly different. F-prob.: P<0.001.

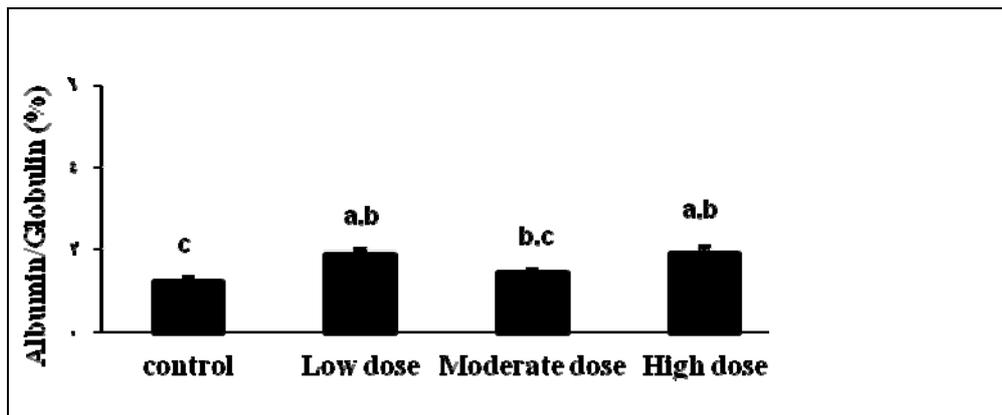


Figure 2: The effect of furfural on in albumin/globulin ratio (A/G ratio) in control, low, moderate and high dose groups. Means, which share the same superscript symbol(s), are not significantly different. F-prob.: P<0.001.

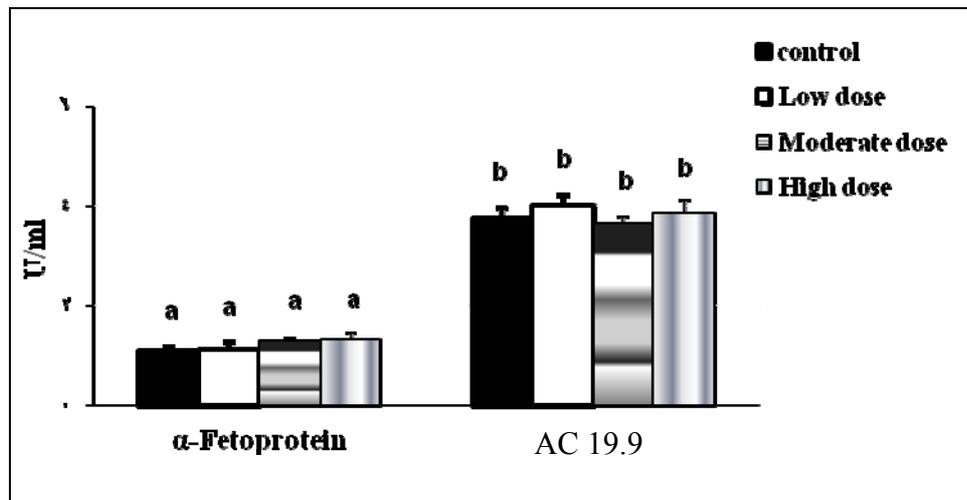


Figure 3: The effect of furfural on Serum  $\alpha$ -fetoprotein (AFP) and carbohydrate antigen (CA)-19.9 in control, low, moderate and high dose groups. Means, which share the same superscript symbol(s), are not significantly different. F-prob.:  $P < 0.001$ .

## DISCUSSION

Furfural has been classified as GRAS (Generally Recognized as Safe) by the Flavor Extract Manufacturers Association (FEMA)<sup>(1)</sup>. The substance 2-furancarboxaldehyde was identified as a high priority for assessment of human health risk because it was considered to present greatest potential for exposure (GPE) and had been classified by other agencies on the basis of carcinogenicity.<sup>(38,39)</sup> The present study shows that the administration of furfural to albino rats for 8 weeks produced significant decrease of red blood corpuscles count, white blood cells (WBC), hematocrit (PCV) and hemoglobin content at the medium

and high doses in a dose dependent manner. However, mean cell volume (MCV) of red blood corpuscles as well as mean cell hemoglobin (MCH) were highly significantly increased as a result of administration of medium and high concentration of furfural in a dose dependent manner. These results were consistent with the findings of **Jonker (2000b)**<sup>(40)</sup> study on Fischer 344 rats were administered microencapsulated furfural via the diet for 13 weeks, there were some hematological changes as decrease in erythrocytes count in males in the highest dose group with increased cell volume and mean corpuscular hemoglobin in the top two dose groups males were observed. The effect may be attributed to effect of

furfural on DNA of the erythropoietic cells which impairs the cell division. Furfural reacts with DNA *in vitro*, primarily at AT base pairs, leading to destabilization of the secondary structure of DNA and to single-strand breaks<sup>(41,42,43)</sup>. Negative<sup>(44)</sup> or weakly positive results<sup>(45)</sup> have been obtained for most bacterial tests for genotoxicity. In particular, positive results were obtained in three out of several assays for reverse mutation in *Salmonella typhimurium* at relatively high concentrations in the absence of metabolic activation. It induced Sister chromatid exchange (SCE) in cultured Chinese hamster ovary (CHO) cells and human lymphocytes<sup>(46)</sup>.

The present study also revealed that, eosinophils percentage was highly significantly depleted as a result of low and medium doses administration. This finding may be attributed to the infiltration of liver by eosinophils as shown by the study of **Shimizu and Kanisawa**<sup>(9,12)</sup> who evidenced the presence of liver damage in the form of scattered eosinophilic globular formation and increase mitotic figures without zonal or massive necrosis observed 6 hours after exposure to furfural by gavage. **Jonker**<sup>(40,47)</sup> in their study, found changes in the perilobular region in 5/10 of all studied rats, mainly, including cells with less coarse cytoplasm and increased clumping of eosinophils<sup>(40,47)</sup>.

The liver synthesizes enzymes and structural proteins, detoxifies many internal and external products of the organism<sup>(48)</sup>. For these functions, hepatocytes use enzyme systems. Furfural is not harmful. However, its by-product, pyromucic acid, has detrimental effect<sup>(49)</sup>. The present

study revealed an increase in the liver enzymes, total bilirubin concentration as well as plasma albumin and albumin/globulin ratio. **Jonker**<sup>(40)</sup> study on Fischer 344 rats that were administered microencapsulated furfural for 13 weeks revealed, in females, a decrease in serum alkaline phosphatase, an increase in gamma glutamyl transferase and an increase in plasma albumin in the highest dose group. In males in the high dose group there was a decrease in ALT, an increase in plasma albumin and albumin/globulin ratio. The increase in liver enzymes as a result of furfural administration could be explained by inflammation and tissue damage induced by furfural effect on the liver hepatocytes.

**Irwin**<sup>(50)</sup> in a subchronic toxicity study revealed that furfural causes centrilobular necrosis and multifocal subchronic inflammation of the liver were observed in males at 150 mg/kg-body weight per day, only, and at 300 mg/kg-body weight per day, the same liver effects were observed both in males and females.

The increase in serum total protein and albumin levels as a result of medium and high doses of furfural in the present study may be explained on the basis liver cirrhosis induced by furfural.

In rat cirrhotic liver, there were no significant differences in levels of serum albumin or albumin mRNA expression between cirrhotic and normal liver. In primary hepatocyte culture, albumin mRNA expression, the amount of albumin secretion and the albumin promoter activity were clearly enhanced in cirrhotic

hepatocytes compared to normal hepatocytes<sup>(14)</sup>.

Serum globulin level, on the other hand, was significantly elevated due only to low dose. This finding was in agreement with the results of the study of **Agakishiev et al.**<sup>(51)</sup> which revealed that application of furfural resulted in imbalanced levels of IgG1, IgG2, IgA, and IgM after exposure of guinea pig skin to furfural.

The use of tumor markers has become a very attractive method for the detection and diagnosis of neoplastic diseases<sup>(52,53)</sup>. However, their value in cancer detection has been controversial largely because no single tumor marker is sensitive and specific enough to meet strict diagnostic criteria<sup>(54)</sup>. **Attallah et al.**<sup>(54)</sup>, in their study showed that CA<sub>19.9</sub> has the best sensitivity for pancreatic cancer. In hepatocellular carcinoma, AFP was the most sensitive tumor marker. The mode of action underlying the hepatocarcinogenic activity of furfural after oral exposure has not fully been elucidated. However, a genotoxic component clearly is not involved, as evidenced by the *in vivo* test using transgenic animals. The data do, however, point to a possible role for chronic cytotoxicity that is found in conjunction with the induction of tumors; a pathway that has also been accepted for other non-genotoxic hepatocarcinogens.

In the present study, we investigated the levels of serum AFP and CA<sub>19.9</sub> as markers for early detection of hepatocellular carcinoma but these levels were non-significantly affected as a result of all tested doses

of furfural. In our study, the serum urea level was highly significantly increased as a result of all tested doses of furfural; The urea/creatinine ratio was only significantly decreased as a result of medium and high doses. However, in the study of **Jonker**<sup>(55)</sup>, female rats at some doses had decreased blood urea nitrogen and creatinine concentrations, but these changes were not dose-related. This may be due to the effect of furfural on the kidney when it is eliminated through it.

## CONCLUSIONS

The administration of furfural to albino rats for 8 weeks produced macrocytic anemia, leucopenia, elevated liver enzymes and bilirubin indicating hepatic damage. Mainly these changes are dose related, but there is no evidence of carcinogenic effect by tumor markers.

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## تأثير مادة الفورفورال كمنكهة طعام على الجوانب الدموية والبيوكيميائية في ذكور الجرذان البيضاء.

طارق محمد على<sup>١</sup> - أسامة محمد أحمد<sup>٢</sup> - رشا أحمد رشاد<sup>٣</sup>  
علم وظائف الأعضاء، كلية الطب<sup>١</sup> - علم وظائف الأعضاء، قسم علم الحيوان، كلية العلوم<sup>٢</sup> -  
لم الأنسجة، قسم علم الحيوان، كلية العلوم - جامعة بني سويف، مصر

### الاهداف

تهدف هذه الدراسة إلى تقييم تأثير مادة الفورفورال، وهي عبارة عن الدهايد شائع الاستخدام كمنكهة طعام في كثير من الأطعمة، على الجوانب الدموية والبيوكيميائية في ذكور الجرذان البيضاء.

### المواد والأساليب

قسمت حيوانات التجارب المستخدمة في هذه الدراسة إلى أربع مجموعات. فقد أعطيت المجموعة الضابطة مادة ثنائي ميثيل السلفوكسيد في حين أعطيت المجموعات الثلاثة الأخرى مادة الفورفورال عن طريق الفم لمدة ٨ أسابيع في جرعة من ٦.٣٦، ٣.١٨ و ١٢.٧٢ ملغ / كغ من وزن الجسم على التوالي. وقد تم الحصول على عينات من الدم لقياس تعداد الدم الكامل وعمل اختبارات وظائف الكبد والكلية والبروتين الجنيني (اف ب) في المصل ومستضد الكربوهيدرات سى ايه ١٩.٩

### النتائج

كشفت النتائج التي تم الحصول عليها عن انخفاض في عدد خلايا الدم الحمراء ومحتوى الهيموجلوبين، وحجم الخلايا الحمراء المعبأة وزيادة في متوسط حجم كرة الدم الحمراء و متوسط محتوى الهيموغلوبيين بكرة الدم الحمراء في الفئران التي عولجت بالفورفورال بطريقة تعتمد على الجرعة. خلايا الدم البيضاء وتناقص في عدد خلايا الدم البيضاء خاصة الكريات البيضاء الحمضة في مجموعات الجرعات المنخفضة والمتوسطة من الفورفورال وقد أدى إعطاء الفورفورال إلى ارتفاع نشاط إنزيمات الكبد في المصل و أيضا مجموع تركيز البيلروبين. و قد زادت مستويات مجموع البروتين والألبومين في المصل في مجموعات الجرعات المتوسطة والعالية، في حين أن مستوى الجلوبيولين ارتفع فقط في مجموعة الجرعات المنخفضة. ووجد أيضا ارتفاع في مستوى البوربا في الدم في حين ان مستويات البروتين الجنيني ألفا ومستضد الكربوهيدرات سى ايه ١٩.٩ في المصل لم تتأثر في جميع الفئات.

### الاستنتاجات

إن إعطاء مادة الفورفورال للفئران في جرعات كبيرة ومدة طويلة قد يؤدي إلى نوع من فقر دم ذي حجم كرات الدم الكبير، نقص الكريات البيض، و انخفاض نسبة خلايا الايزينوفيل وارتفاع إنزيمات الكبد والبوربا في الفئران بطريقة مرتبطة بالجرعة.